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ERRATA.

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Page	Line	
602	3	*for* "**284**" *read* "**284**".
1158	4	*for* "absorbed in" *read* "adsorbed on"
1159		In equation (2), *for* "ν_1" *read* "ν'".
1163	17	*for* "of" *read* "or".
1163	41	*for* "Oreyer" *read* "Dreyer".

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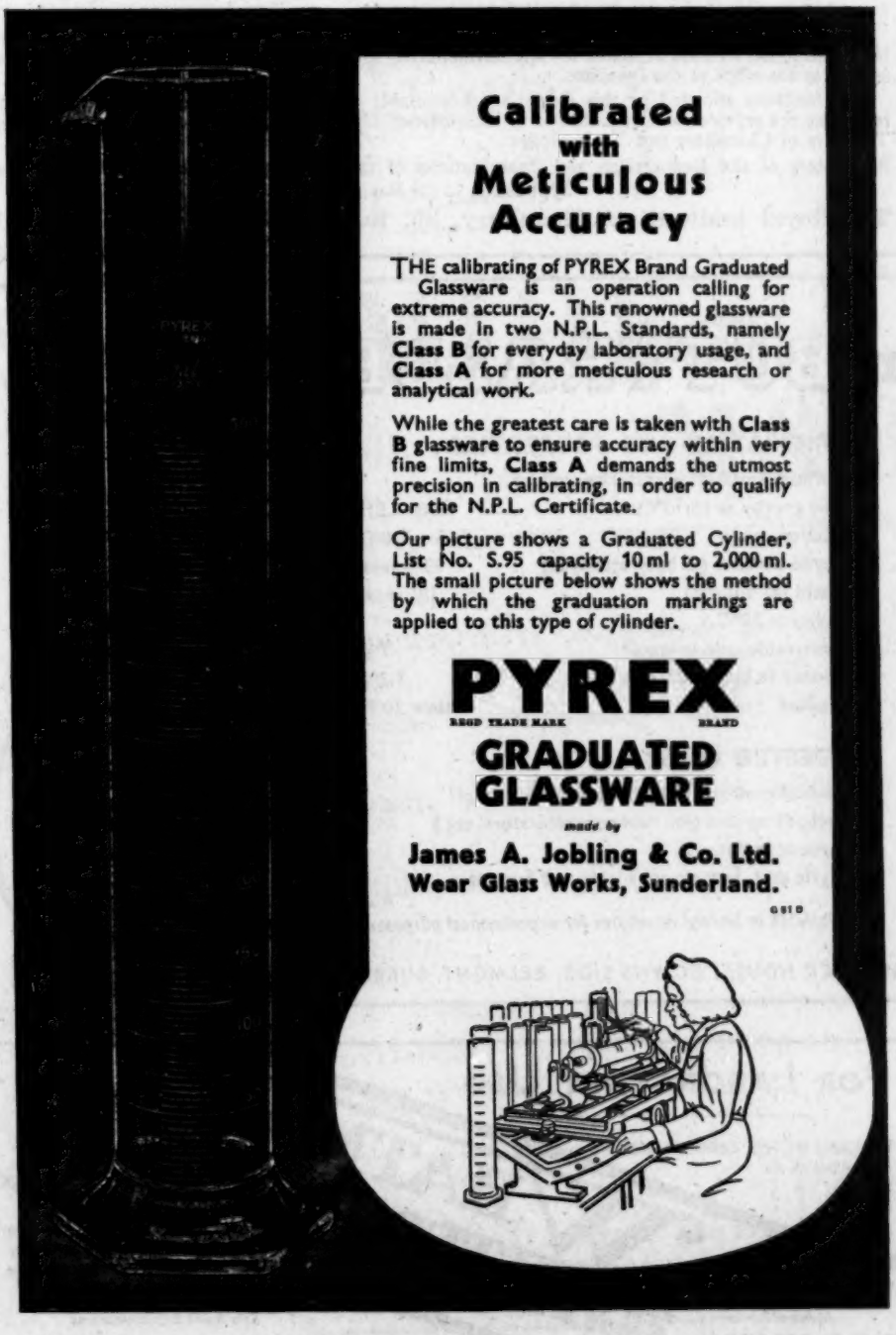
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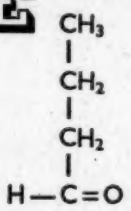

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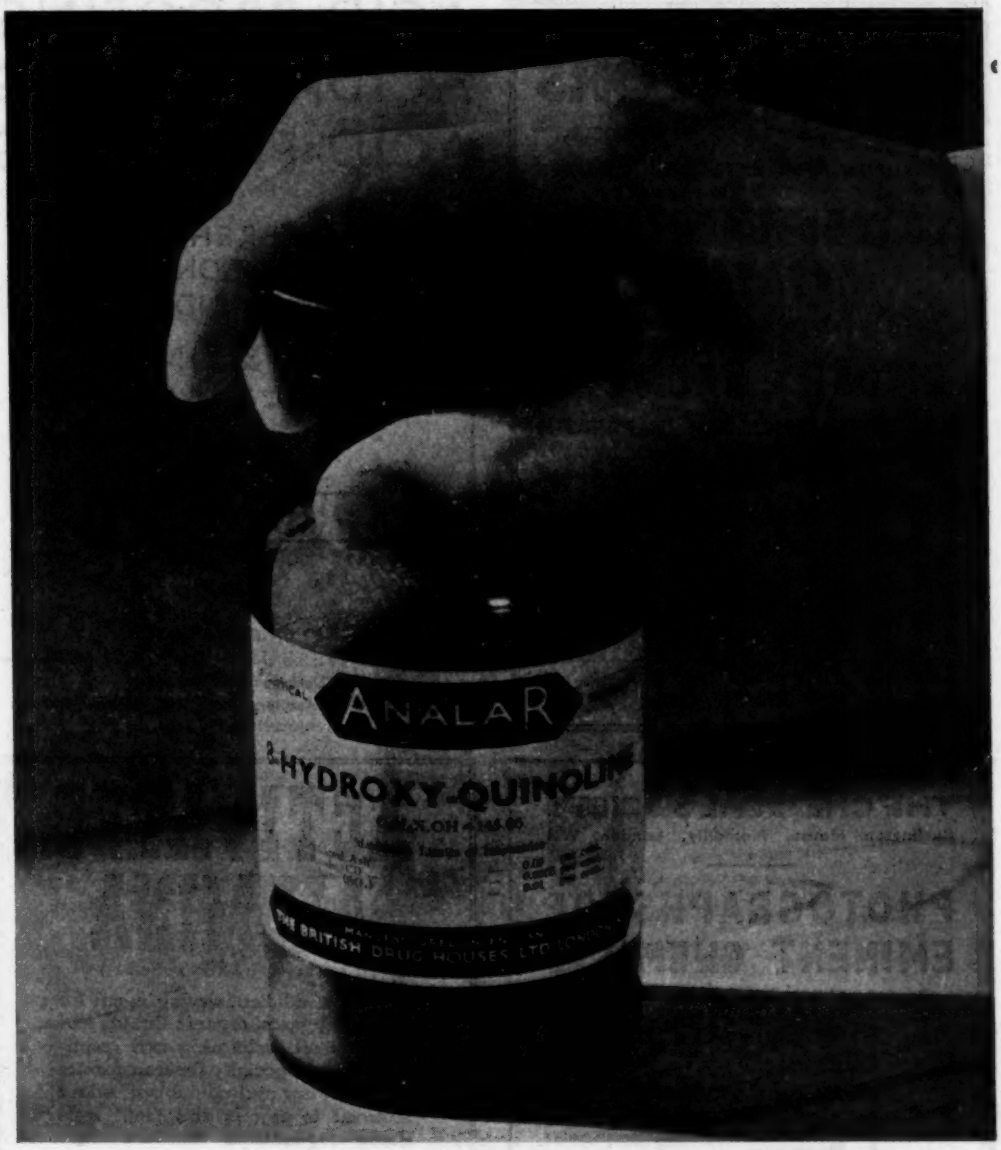

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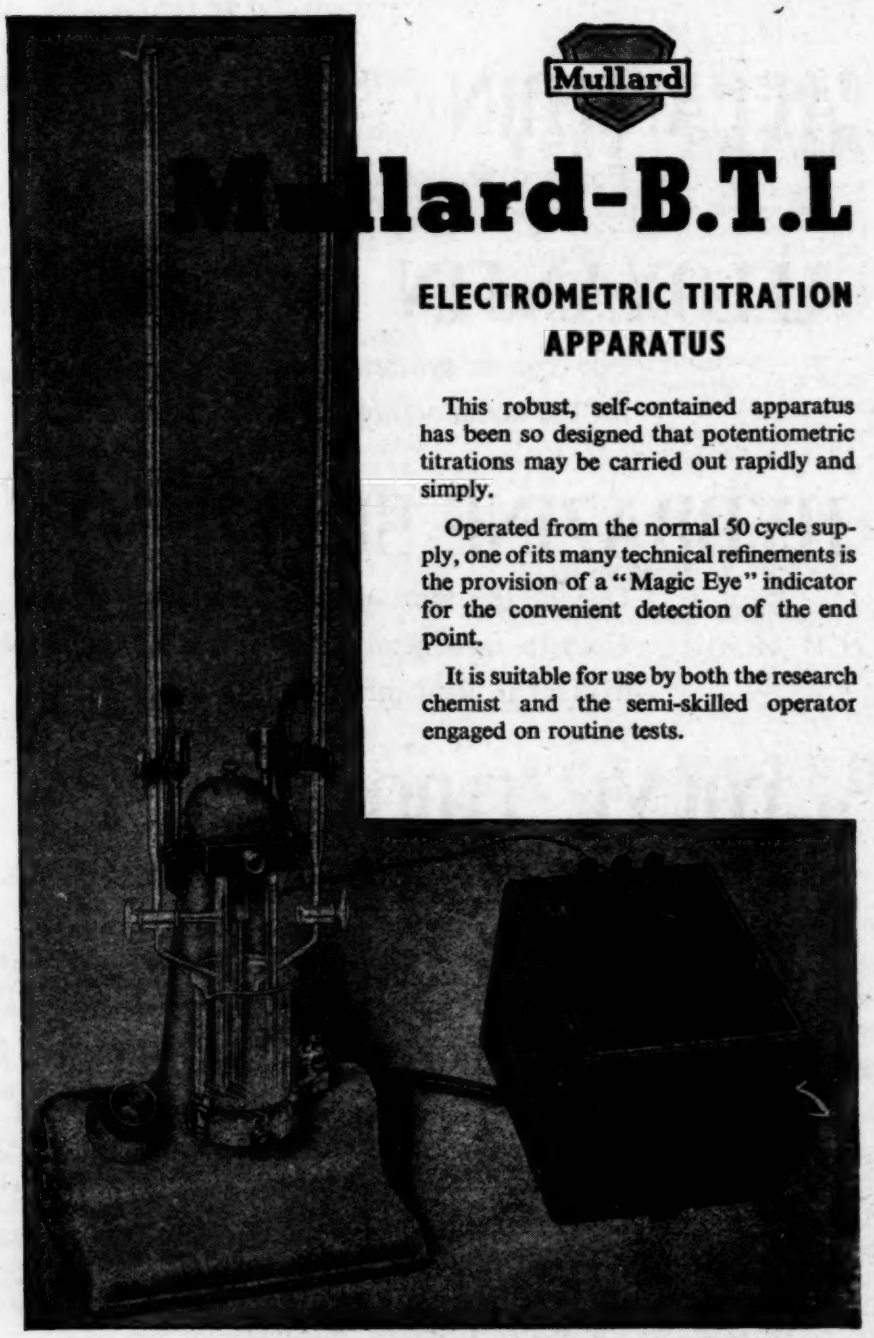

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The polysaccharide from the waxy layer was bound in a novel complex which had some interesting serological properties. This complex was possibly an antigen which, in addition to the polysaccharide (*a*), contained (*b*) an acid-fast lipoid material, (*c*) deoxyribonucleic acid, and (*d*) a small amount of a peptide constituent, and it could be obtained only from the intact cells. The complex was extracted at 37° as shown in Figure 8 by organic lipophilic bases (including urea and β-hydroxypropionamidine), further fractionated with organic bases, and finally isolated by being dried from the frozen state.

For the serological tests the materials, *e.g.*, Complexes A and B, were both separately coated on to a colloidal suspension of collodion particles and then tested against the sera of tuberculous and normal humans. The tests were carried out by Dr. Nassau of the Harefield Sanatorium and are being extended elsewhere. The collodion particles coated with Complex A and B give a good agglutination under appropriate conditions with sera from tuberculous patients, and already the results appear to show promise in diagnosis apart from any possible value in immunisation. It is of interest to note that no antigenic material could be obtained from defatted cells.

Other complex carbohydrates of high biological significance are the specific blood group factors, an account of which has been given by Stacey in "Advances in Carbohydrate Chemistry". Group A resembles the tuberculosis polysaccharides in possessing branched chain structures with glucosamine, mannose, and galactose, as constituent units. A specimen examined (Bray, Henry, and Stacey, *Biochem. J.*, 1946, 124) contained a methylpentose end-group, namely L-fucose, which thus differed significantly from the L-rhamnose end group in the tubercle polysaccharide described above.

It will be seen that many projects in the carbohydrate field still await the attention of workers interested in the problems of infectious disease processes, and it is worthy of mention that American investigators have isolated from the important antibiotic, streptomycin, the optical enantiomorph of glucosamine, namely the L-isomer.

Appendix.

	Identified products of acid hydrolysis of carbohydrate portion.
1. *Containing hexosamine and hexuronic acid.*	
(a) Sulphate-free.	
(i) Hyaluronic (from vitreous humour, umbilical cord, synovial fluid, ovarian tumour, Group "A" hæmolytic *Streptococcus* and skin).	*N*-Acetyl D-glucosamine Hexuronic acid (probably D-glucuronic acid)
(ii) Type I *Pneumococcus* specific polysaccharide.	Acetic acid Hexosamine D-Galacturonic acid
(b) Sulphate-containing.	
(i) Heparin.	Sulphuric acid D-Glucuronic acid D-Glucosamine (unacetylated)
(ii) Chondroitin sulphate.	*N*-Acetyl chondrosamine Sulphuric acid D-Glucuronic acid
(iii) Mucoitin sulphate (from gastric mucin).	*N*-Acetyl D-glucosamine Hexuronic acid Sulphuric acid
(iv) Hyaluronic acid sulphate (from the cornea).	Sulphuric acid *N*-Acetyl hexosamine Hexuronic acid
2. *Containing hexosamine but no hexuronic acid.*	
(a) Chitin.	*N*-Acetyl D-glucosamine
(b) Bacterial.	
(i) *Pneumococcus* "C" (or Group) polysaccharide.	*N*-Acetyl amino-sugar D-Glucose
(ii) Type IV *Pneumococcus* specific polysaccharide.	*N*-Acetyl amino-sugar D-Glucose
(iii) Type XIV specific polysaccharide.	*N*-Acetyl D-glucosamine D-Galactose
(c) Blood Group.	
(i) Blood Group A carbohydrate (from saliva, pepsin, urine, gastric mucin, pancreas, etc.).	*N*-Acetyl D-glucosamine D-Mannose D-Galactose L-Fucose
(ii) Blood Group B and O carbohydrates from human saliva and gastric mucin.	Hexosamine

107. *The Conversion of Sucrose into Thiazole Derivatives. Part I. Sulphanilamidothiazoles Derived from Lævulic Acid.*

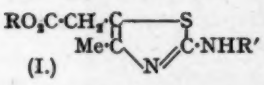
By Hilda Gregory and L. F. Wiggins.

Lævulic acid has been converted into *2-sulphanilamido-4-methylthiazole-5-acetic acid* and its *ethyl* ester. The former has the greater *in vitro* antibacterial activity and forms very soluble sodium and calcium salts. A number of basic salts of certain thiazole derivatives are described.

It is well established that sulphathiazole and some of its derivatives are among the most successful of the sulphanilamide drugs in use today. However, sulphathiazole has the disadvantage of low solubility in water; its *N*-acetyl derivative is still less soluble, and it is the latter compound which, formed during the detoxication process in the body, is the cause of the renal disorders which sometimes follow sulphathiazole therapy.

Sulphanilamidothiazoles and *N*-acetylsulphanilamidothiazoles, which are more soluble in water, are of special interest, and two are now described. Sulphanilamidothiazoles which do possess this increased solubility have now been prepared from sucrose through lævulic acid as the essential intermediate.

Ethyl β-bromolævulate (Conrad and Guthzeit, *Ber.*, 1884, **17**, 2285) by condensation with thiourea furnishes ethyl 2-amino-4-methylthiazole-5-acetate (I; R = Et, R′ = H) and hydrolysis of this compound with barium hydroxide solution gave the acid (I; R = R′ = H) which alternatively is obtained by condensation of β-bromolævulic acid with thiourea. Attempts to prepare 2-N^4-acetylsulphanilamido-4-methylthiazole-5-acetic acid from it by condensation with *N*-acetylsulphanilyl chloride were unsuccessful, indicating the zwitterionic character of the thiazole amino-acid. The condensation, however, proceeded smoothly when carried out with the ester (I; R = Et, R′ = H) and gave *ethyl* 2-N^4-*acetylsulphanilamido-4-methylthiazole-5-acetate*. This on hydrolysis with dilute hydrochloric acid gave 2-*sulphanilamido-4-methylthiazole-5-acetic acid hydrochloride*, from which the free *base* (I; R = H, R′ = *p*-$NH_2 \cdot C_6H_4 \cdot SO_2$) was obtained by warming it with water. The solubility of this was 0·113 g./100 c.c. of solution as compared with 0·04 g./100 c.c. of solution for sulphathiazole itself. Moreover, the new compound formed sodium and calcium salts which were very soluble in water.



(I.)

Ethyl 2-sulphanilamido-4-methylthiazole-5-acetate (I; R = Et, R′ = *p*-$NH_2 \cdot C_6H_4 \cdot SO_2$) was eventually obtained by condensation of ethyl 2-amino-4-methylthiazole-5-acetate with *p*-nitrobenzenesulphonyl chloride to give *ethyl* 2-p-*nitrobenzenesulphonamido-4-methylthiazole-5-acetate*, which, by catalytic hydrogenation over Raney nickel, was converted into (I; R = Et, R′ = *p*-$NH_2 \cdot C_6H_4 \cdot SO_2$). This could, by acetylation, be converted into the *N*-acetyl sulphanilamide derivative originally obtained by condensation of *N*-acetylsulphanilyl chloride with ethyl 2-amino-4-methylthiazole-5-acetate.

Compound.	Blood media.	Hartley's broth media.					
	Streptococcus hæmolyticus.	*Streptococcus hæmolyticus.*	*Escherichia coli.*	*Proteus vulgaria.*	*Pseudomonas aeroginosa.*	*Streptococcus aureus.*	*Clostridium welchii.*
Ethyl 2-*p*-nitrobenzenesulphonamido-4-methylthiazole-5-acetate	10	7	>50	—	—	—	—
Ethyl 2-sulphanilamido-4-methylthiazole-5-acetate	5	10	5	>100	>100	>100	>100
2-Sulphanilamido-4-methylthiazole-5-acetic acid	2	5	50	>100	>100	>100	30
Sulphathiazole	0·3	15	5	10	5	>100	5

Figures refer to mg. of material per 100 c.c. necessary to stop the growth of the organism under standardised conditions.

Results of some interest were obtained when the salts of these thiazole derivatives were prepared. In general, monohydrochlorides were produced, even in the case of ethyl 2-amino-4-methylthiazole-5-acetate, 2-amino-4-methylthiazole-5-acetic acid and ethyl 2-sulphanilamido-4-methylthiazole 5-acetate, in all of which there are two potentially basic centres. Since both

ethyl 2-N^4-acetylsulphanilamido-4-methylthiazole-5-acetate and ethyl 2-*p*-nitrobenzenesulphonamido-4-methylthiazole-5-acetate form salts, it is probable that it is the nitrogen atom in the ring which is involved in salt formation. The behaviour of 2-sulphanilamido-4-methylthiazole-5-acetic acid is anomalous in so far as it forms a dihydrochloride even though this is not stable and loses hydrogen chloride on keeping. It would have been more readily explicable had ethyl 2-sulphanilamido-4-methylthiazole-5-acetate formed a mono-salt, since then the difference might have been attributable to the zwitterion effect.

2-Sulphanilamido-4-methylthiazole-5-acetic acid and its ethyl ester and also ethyl 2-(*p*-nitrobenzenesulphonamido)-4-methylthiazole-5-acetate have been tested *in vitro* for their bacteriostatic action, and the results are shown on p. 590 in comparison with sulphathiazole itself.

These results show that 2-sulphanilamido-4-methylthiazole-5-acetic acid shows some promise as a chemotherapeutic agent since its bacteriostatic activity is quite appreciable and its solubility properties show such advantages over sulphathiazole. It is of interest to note that ethyl 2-*p*-nitrobenzenesulphonamido-4-methylthiazole-5-acetate, although it does not possess the sulphanilamido-grouping as such, does show some activity.

Experimental

Ethyl 2-Amino-4-methylthiazole-5-acetate.—This was prepared by the method of Conrad and Schmidt (*Annalen*, 1895, **285**, 203) using a slight excess of thiourea (4·0 g.) in water (30 c.c.) and ethyl β-bromolævulate (11·15 g.) in alcohol (20 c.c.). It was obtained in nearly colourless needles on recrystallisation from 80% aqueous alcohol, m. p. 123° (4·06 g.; 40·6%). The *hydrochloride* was obtained by passing dry hydrogen chloride into a solution of the base in sodium-dried ethyl alcohol at 0° until saturation was complete. Ether was then added, and the crystals which separated recrystallised from ethyl alcohol–ether in shining, colourless plates, m. p. 150° (Found: C, 40·7; H, 5·0; N, 11·7. $C_8H_{12}O_2N_2S$,HCl requires C, 40·60; H, 5·5; N, 11·9%).

2-Amino-4-methylthiazole-5-acetic Acid.—(*a*) The above ester (1·0 g.) was heated over a gauze for 3 hours with twice the calculated amount of barium hydroxide in water (75 c.c.). The mixture was then cooled and 5N-sulphuric acid added carefully until all the barium had been precipitated. Some slight decomposition of the thiazole derivative occurred during neutralisation as indicated by the evolution of hydrogen sulphide. The barium sulphate was filtered off and the aqueous solution concentrated under reduced pressure to small bulk. On cooling, crystals separated which, recrystallised from water in needles, had m. p. 274—275°, and were identical with the 2-amino-4-methylthiazole-5-acetic acid obtained below (0·55 g.; 63·9%).

(*b*) The acid was prepared according to the method of Conrad and Schmidt (*loc. cit.*) from thiourea (4·0 g.; 1·1 moles) and β-bromolævulic acid (10 g.). Recrystallisation from water gave the acid (5·0 g.; 56·7% of theory), m. p. 275° (Conrad and Schmidt give m. p. 259—260°) (Found: C, 42·1; H, 5·0; N, 16·2. Calc. for $C_6H_8N_2SO_2$: C, 41·9; H, 4·7; N, 16·3%). The *hydrochloride* was obtained by heating the acid with 5N-hydrochloric acid for a few minutes. On cooling, crystals separated which were recrystallised from water containing a little dilute hydrochloric acid; m. p. 228° (Found: C, 34·4; H, 4·6; N, 13·6. $C_6H_8N_2O_2S$,HCl requires C, 34·5; H, 4·4; N, 13·4%).

Ethyl 2-N^4-Acetylsulphanilamido-4-methylthiazole-5-acetate.—To ethyl 2-amino-4-methylthiazole-5-acetate (4·0 g.) in dry pyridine (40 c.c.) was added *N*-acetylsulphanilyl chloride (5·16 g., 1·1 moles) in dry pyridine (16 c.c.) at 0°. After 24 hours at room temperature, the reaction mixture was poured into ice-cold water and acidified with dilute hydrochloric acid at 0° (Congo-red). The *product* gradually separated during several hours as a fine crystalline powder. It recrystallised from aqueous alcohol in fine cream crystals, m. p. 203—204° (5·65 g.; 71·14%) (Found: C, 48·6; H, 4·7; N, 10·6. $C_{16}H_{19}O_5N_3S_2$ requires C, 48·4; H, 4·8; N, 10·6%). An early attempt to purify the crude product by suspending it in water, adding 5N-ammonia until the solution was alkaline to thymol blue, and refluxing the resulting reddish-brown solution with decolorising charcoal for ½ hour, gave a straw-coloured solution which, when cooled to 0° and acidified with dilute hydrochloric acid, yielded crystals of *2-N^4-acetylsulphanilamido-4-methylthiazole-5-acetic acid* (Found: C, 45·3; H, 4·5; N, 11·1. $C_{14}H_{15}O_5N_3S_2$ requires C, 45·5; H, 4·1; N, 11·4%); this, after recrystallisation from alcohol, had m. p. 228° and depressed the m. p. of the ethyl ester.

Ethyl 2-N^4-Acetylsulphanilamido-4-methylthiazole-5-acetate hydrochloride was prepared by dissolving the free base in sodium-dried ethyl alcohol and saturating the solution with dry hydrogen chloride at 0°. The salt, which separated on addition of ether, crystallised from ethyl alcohol–ether in colourless crystals, m. p. 206—207° (Found: C, 43·8; H, 5·0. $C_{16}H_{19}O_5N_3S_2$,HCl requires C, 44·3; H, 4·7%).

Hydrolysis of Ethyl 2-N^4-Acetylsulphanilamido-4-methylthiazole-5-acetate.—(a) *Using 2N-hydrochloric acid.* The acetyl derivative (5·0 g.) was suspended in 2N-hydrochloric acid (50 c.c.) and dissolved by heating on a water-bath for 1 hour. On cooling, fine colourless needles separated. These were collected and recrystallised from N-hydrochloric acid, giving long colourless needles of *2-sulphanilamido-4-methylthiazole-5-acetic acid dihydrochloride*, m. p. 235—236° (decomp.). Yield, 4·57 g., increased to 4·87 g. (theoretical) by working up the mother liquors (Found: C, 36·4; H, 3·9; N, 10·7. $C_{12}H_{13}O_4N_3S_2$,2HCl requires C, 36·0; H, 3·8; N, 10·5%). Under anhydrous conditions the dihydrochloride slowly decomposed and after 3 months it analysed as a *monohydrochloride* (Found: C, 39·0; H, 4·17; Cl, 10·6. $C_{12}H_{13}O_4N_3S_2$,HCl requires C, 39·6; H, 3·9; Cl, 9·8%).

(b) *Using 10% sodium hydroxide.* The acetyl derivative (1·0 g.) in 10% sodium hydroxide (10 c.c.) was heated on a water-bath for 2 hours, allowed to cool, and treated with excess of 5N-hydrochloric acid. The crystals which separated were recrystallised from N-hydrochloric acid and were identical with the product obtained in (a); m. p. 235—236° (0·80 g.; 83·4%).

Reacetylation of 2-Sulphanilamido-4-methylthiazole-5-acetic Acid Hydrochloride.—To the amine hydrochloride (0·1 g.), suspended in dilute acetic acid (5 c.c.), was added acetic anhydride (5 c.c.), and the mixture shaken until a clear solution was obtained. After a few minutes crystals separated, which were collected and recrystallised from ethyl alcohol; m. p. alone or in admixture with the 2-N^4-acetylsulphanilamido-4-methylthiazole-5-acetic acid previously described, 228°.

2-Sulphanilamido-4-methylthiazole-5-acetic Acid.—The hydrochloride (m. p. 235—236°; 1·5 g.) was suspended in water (50 c.c.) and dissolved by refluxing on a wire gauze for 1 hour. The crystals which separated on cooling were recrystallised from water giving colourless flakes of *2-sulphanilamido-4-methylthiazole-5-acetic acid*, m. p. 246—247° (1·1 g.; 86·3%) (Found: C, 43·9; H, 3·8; N, 12·5; NH_2 by nitrite titration, 4·88. $C_{12}H_{13}O_4N_3S_2$ requires C, 44·0; H, 4·0; N, 12·8; NH_2, 4·9%).

Ethyl 2-p-Nitrobenzenesulphonamido-4-methylthiazole-5-acetate.—*p*-Nitrobenzenesulphonyl chloride (2·5 g.; 1·1 moles) dissolved in dry pyridine was slowly added at 0° to ethyl 2-amino-4-methylthiazole-5-acetate (2·0 g.) also in dry pyridine (20 c.c.). After 12 hours at room temperature the reddish-brown solution was poured into ice-cold water and acidified to Congo-red at 0° with dilute hydrochloric acid. The crude product which separated recrystallised from acetone in long, yellow needles of the *ester*, m. p. 186—187° (2·8 g.; 94·9%) (Found: C, 43·9; H, 3·9; N, 11·4. $C_{14}H_{15}O_6N_3S_2$ requires C, 43·6; H, 3·9; N, 10·90%). The *hydrochloride* was prepared by dissolving the ester (0·05 g.) in dry methyl alcohol, and saturating the solution with dry hydrogen chloride at 0°. On slow evaporation of the solution in a vacuum desiccator, crystals separated and were recrystallised from anhydrous methyl alcohol containing dry hydrogen chloride; m. p. 236° (Found: C, 40·1; H, 3·9. $C_{14}H_{15}O_6N_3S_2$,HCl requires C, 39·9; H, 3·8%).

Ethyl 2-Sulphanilamido-4-methylthiazole-5-acetate.—2-*p*-Nitrobenzenesulphonamido-4-methylthiazole-5-acetate (1·0 g.) was dissolved in methyl alcohol (150 c.c.) and hydrogenated over Raney nickel at room temperature. After filtration and evaporation of the solvent, the crude product was recrystallised from acetone–water; needles of ethyl 2-sulphanilamido-4-methylthiazole-5-acetate containing acetone of crystallisation were thereby obtained, m. p. 184° (0·7 g.; 75·9%). After several days at room temperature the crystals had changed in form with conversion into the anhydrous *compound*, m. p. 137°; solubility in water was found to be 0·04725 g./100 c.c. solution (Found: C, 47·3; H, 4·9; N, 11·8; NH_2 by nitrite titration, 4·51. $C_{14}H_{17}O_4N_3S_2$ requires C, 47·34; H, 4·8; N, 11·8; NH_2, 4·51%).

The *monohydrochloride* was obtained by dissolving the free base in sodium-dried ethyl alcohol and saturating the solution with dry hydrogen chloride at 0°. The solution was then evaporated to dryness in a vacuum desiccator and the crude salt recrystallised from ethyl alcohol–ether to give fine colourless flakes, m. p. 228° (Found: C, 42·4; H, 4·7; N, 10·9. $C_{14}H_{17}O_4N_3S_2$,HCl requires C, 42·8; H, 4·6; N, 10·7%).

Acetylation of Ethyl 2-Sulphanilamido-4-methylthiazole-5-acetate.—Acetic anhydride (5 c.c.) was added to the free base (0·1 g.) suspended in 5 c.c. of dilute acetic acid. After being shaken until a clear solution was obtained the mixture was kept for 24 hours at room temperature and then poured into ice-cold water. The product slowly separated on standing, and when recrystallised from aqueous alcohol was identical with the ethyl 2-N^4-acetylsulphanilamido-4-methylthiazole-5-acetate, m. p. 203—204°, obtained previously.

The authors wish to express their thanks to Professor W. N. Haworth, F.R.S., and Dr. J. L. Simonsen, F.R.S., for their interest in this work, and to the Colonial Products Research Council for financial assistance. They also wish to thank Dr. C. R. Harington, F.R.S., Director of the National Institute for Medical Research, for the bacteriostatic tests.

THE A. E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15. [*Received, July 11th*, 1946.]

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108. 2 : 3-*Dimercaptopropanol* ("*British Anti-Lewisite*") *and Related Compounds.*

By L. A. STOCKEN.

The preparation of several aliphatic dithiols and in particular of pure 2 : 3-dimercaptopropanol is described, together with their condensation products with carbonyl compounds and dichloroarsines.

FUNDAMENTAL work on the reaction between arsenical compounds and proteins (Stocken and Thompson, 1940, Report to the Ministry of Supply by Peters, No. 20) suggested that the toxicity of arsenic to living cells is due to its combination with two neighbouring thiol groups in an essential enzyme to form a stable ring. The consequence of this hypothesis was the possibility that 1 : 2- or 1 : 3-dithiols might displace arsenic from tissue receptors by giving more stable five- or six-membered rings and would thus constitute antidotes to arsenical war gases. Preliminary experiments with toluene-3 : 4-dithiol and ethanedithiol indicated that this type of compound was indeed capable of affording effective protection *in vitro* and *in vivo* against the toxic action of "lewisite"'. It was found, however, that neither of these substances satisfied certain conditions desirable in an antidote for field application against skin contamination, and it was necessary, therefore, to prepare other compounds having 1 : 2- or 1 : 3-dithiol

substitution. For reasons explained elsewhere (Stocken and Thompson, *Biochem. J.*, 1946, **40**, 535) the search was confined to compounds of low molecular weight and preferably to those which had a hydrophilic group. Since, in the event of equal therapeutic efficiency, the final choice of antidote depended on toxicity, a few typical compounds were synthesised with the hope of making generalisations about their properties. From this work it seemed that aryl- and 1 : 3-dithiols were the least satisfactory and that 2 : 3-*dimercaptopropanol* (subsequently called " British Anti-Lewisite " or " BAL ") was sufficiently superior to the others to justify its manufacture on a large scale.

Of the many methods available for the preparation of thiols, only the reaction between the halogen compound and ammonium or metal hydrogen sulphide gave good results when applied to the production of dithiols. Even this reaction was unsatisfactory unless a closed system was used to avoid sulphide formation (cf. Meadow and Reid, *J. Amer. Chem. Soc.*, 1934, **56**, 2177), and 2 : 3-dimercaptopropylamine could only be obtained by means of ammonium hydrogen sulphide. The use of this sulphide for the preparation of thiols is apparently new, and it possesses certain advantages over the metal hydrogen sulphides. Ammonium hydrogen sulphide is more soluble (20% in methanol), the excess remaining at the end of the reaction is conveniently removed by evacuation of the vessel, and the product is much cleaner. In the preparation of BAL several variants of the hydrogen sulphide process were tried, but since a more detailed investigation was subsequently carried out by Gasson, Millidge, Woodward, *et al.* (Sutton Oak reports 1942 and 1943) only the two most effective are described here.

Although the analytical figures indicated that only a small amount of impurity could be present, some evidence gained from the preparation of acetals suggested that laboratory specimens of BAL were not absolutely pure. A further purification was effected by partition between water and an excess of the dithiol, but the efficacy of the method was not reflected by any significant change in the analytical figures. It was considered, therefore, that some supplementary test was required, especially when a sample from the U.S.A. (prepared by a catalytic process and having satisfactory analytical figures) was found to be unduly toxic. Chromatography gave no indication of the presence of a contaminant in the water-purified BAL which was used as a standard. A comparison of the physical constants of preparations obtained from four sources (see Table) revealed little or no difference in refractive index or density but did show a significant difference in viscosity and solubility in water. Subsequent to the completion of this work Sjöberg (*Ber.*, 1942, **75**, 13) described the preparation of 2 : 3-dimercaptopropanol, which he purified by means of the mercury derivative. The dithiol was then distilled at low pressure, to give an overall yield of 14%.

Physical constants of various specimens of 2 : 3-*dimercaptopropanol at* 20°.

	d.	n_D.	η.*	Solubility (w/v, %).
I.C.I. preparation (semi-large scale)	1·2578	1·5749	1·494	5·9
U.S.A. catalytic preparation	1·2427	1·5767	0·7333	5·6
Sutton Oak (laboratory preparation)	1·2472	1·5749	1·018	6·4
Oxford (purified)	1·2463	1·5733	1·000	6·8

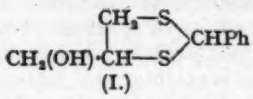
* Relative to purest Oxford sample.

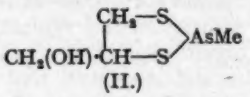
Unfortunately, the hydrogen sulphide method cannot be applied when other reactive substituents are present. An attempt was therefore made to protect the dithiol groups, to carry out further synthetic steps, and then as a final stage to regenerate the thiol. Thioacetals were prepared, but at the time this work was reported to the Ministry of Supply (Stocken, Thompson, and Whittaker, 1942, Report to Ministry of Supply by Peters, No. 52; Stocken and Thompson, 1943, Report to Ministry of Supply by Peters, No. 64) no success had been achieved. More recently, however, it has been found that 2 : 3-*bisbenzylthiopropanol*, 2-*phenyl*-4-*hydroxymethyl*-1 : 3-*dithiolan* (I), and 2-*methyl*-4-*hydroxymethyl*-1 : 3-*dithia*-2-*arsa*cyclo*pentane* (II) can be reduced in the presence of ethanol by sodium in liquid ammonia to give excellent yields of 2 : 3-dimercaptopropanol.

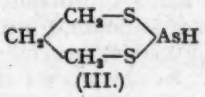
In view of the structural similarity of 2 : 2'-dichlorodiethyl sulphide (" mustard gas ") to 2-*methyl*-4-*chloromethyl*-1 : 3-*dithiolan* and 2 : 2-*dimethyl*-4-*chloromethyl*-1 : 3-*dithiolan*, it was expected that these compounds might possess some vesicant power, but they were found to have only 2% and 1% of the absolute vesicancy of mustard gas.

Since only two cyclic thioarsinites have so far been described (Cohen, King, and Strangeways, *J.*, 1931, 3043), both of which were derived from ethanedithiol, 2-chlorovinyl-, phenyl-, and methyl-dichloroarsines were condensed with the 1 : 2- and 1 : 3-dithiols, the latter giving rise to 1 : 3-*dithia*-2-*arsa*cyclo*hexane* (III).

An attempt made to prepare the open chain thioarsinites from bis-2-chlorovinylchloroarsine and the dithiols was abandoned, since the products decomposed on distillation.


(I.)


(II.)


(III.)

Experimental.

The sodium hydrogen sulphide solution was prepared by dissolving sodium (5 g.) in ethanol (100 c.c.) and saturating with dry hydrogen sulphide at 0—5°, and the ammonium hydrogen sulphide by passing dry ammonia and hydrogen sulphide into ether (sodium dried) at 0°.

Ethane-, 1 : 2-*Propane-*, 1 : 3-*Propane- and* 1 : 5-*Pentane-dithiols.*—The appropriate dihalide (1 mol.) was heated with sodium hydrogen sulphide (6 mols.) in ethanol for 12 hours in a closed vessel at 80—90°. Since these dithiols distil with the ethanol, 10N-sodium hydroxide (6 mols.) was added to the reaction product before evaporation of the ethanol under reduced pressure. The residue was then acidified to Congo-red with hydrochloric acid (external cooling), and sodium chloride was removed by filtration. The dithiol which separated was combined with a single ether extract of the aqueous layer, dried (Na_2SO_4), and, after removal of the solvent, distilled. The yields were 55—65%.

1 : 3-*Dimercaptopropanol.* 1 : 3-Dibromohydrin (0·1 mol.) was heated at 80—90° with sodium hydrogen sulphide (0·6 mol.) in ethanol for 12 hours in a pressure bottle. After acidification of the reaction mixture the ethanol was removed under reduced pressure, and sufficient water added to dissolve the sodium chloride; chloroform was used to extract the dithiol. Yield, 65%; b. p. 80°/1·0 mm. Rheinboldt and Tetsch (*Ber.*, 1937, **70**, 675) give b. p. 94°/12 mm. in a stream of carbon dioxide (Found: S, 51·4; SH, 53·0. Calc. for $C_3H_8OS_2$: S, 51·6; SH, 53·2%). Propane-1 : 2 : 3-trithiol was prepared similarly. Yield, 50%; b. p. 95°/1·0 mm. (Found: SH, 70·8. Calc. for $C_3H_8S_3$: SH, 70·8%).

2 : 3-*Dimercaptopropylamine.* 2 : 3-Dibromopropylamine hydrochloride (40 g.) was heated in a pressure bottle with ammonium hydrogen sulphide (120 g. in 600 c.c. of methanol) for 16 hours at 80—90°. The excess of hydrogen sulphide and alcohol was then removed under reduced pressure, and the residue was taken up in the minimum volume of dilute ammonia. The solution was then extracted many times with benzene. The extract was dried (Na_2SO_4), filtered, and evaporated. The residue was distilled at low pressure. Yield, 8 g. (40%), b. p. 80°/1·0 mm. (Found: S, 52·3. $C_3H_9NS_2$ requires S, 52·0%).

Methyl 2 : 3-*dimercaptopropyl ether* was obtained from methyl 2 : 3-dibromopropyl ether by the method described for 1 : 3-dimercaptopropanol. Yield, 50%; b. p. 68°/1·0 mm. (Found: S, 46·0. $C_4H_{10}OS_2$ requires S, 46·4%).

2 : 3-*Dimercaptopropanol* (" *British Anti-Lewisite* "). 2 : 3-Dibromohydrin (1 kg.) was allowed to react for several days at room temperature with sodium hydrogen sulphide solution (12·6 l.) in a closed vessel filled to capacity. The usual process was employed for the isolation of the *compound*. Yield, 366 g. (64%). There was no significant alteration in yield when the alternative higher temperature method was used, but the available apparatus limited the absolute yield to about 26 g.

" Crude " 2 : 3-dimercaptopropanol (360 g.) was shaken with distilled water (4 l.) for 3 hours at room temperature, and then allowed to settle overnight. The supernatant layer was filtered through two No. 1. Whatman filter papers to remove oily globules; ammonium sulphate (1900 g.) was added to the filtrate which was then extracted with benzene (1 l.) (Stocken and Thompson, 1943, Report to Ministry of Supply by Peters, No. 65; Peters, Stocken and Thompson, Report to Ministry of Supply by Peters, No. 77). The benzene extract was dried (Na_2SO_4), filtered, evaporated under reduced pressure (40—50°), and the residue distilled in a high vacuum. The middle 80% was taken for examination although there was neither a low- nor a high-boiling fraction. This experiment was repeated several times in order to obtain 1 l. of a standard preparation (Found: C, 28·6 *; H, 6·53 *; S, 51·7; SH, 53·5. $C_3H_8OS_2$ requires C, 29·0; H, 6·55; S, 51·6; SH, 53·2%).

Condensation Products of Dithiols with Carbonyl Compounds.—2 : 3-Dimercaptopropanol (124 g.) mixed with benzaldehyde (106 g.) in benzene (300 c.c.) and a few drops of concentrated hydrochloric acid reacted exothermically to give 2-*phenyl*-4-*hydroxymethyl*-1 : 3-*dithiolan* which was isolated after removal of water by crystallisation from benzene–light petroleum (b. p. 60—80°). Yield, 200 g.; m. p. 77°; b. p. 207°/1·5 mm. (slight decomp.) (Found: S, 30·4. $C_{10}H_{12}OS_2$ requires S, 30·2%). Benzaldehyde and 1 : 3-dimercaptopropanol were condensed in the same way as described for the isomer and the 2-*phenyl*-4-*hydroxy*-1 : 3-*dithian* crystallised from benzene. Yield, almost quantitative; m. p. 142—143° (Found: S, 30·3. $C_{10}H_{12}OS_2$ requires S, 30·2%). 2-Phenyl-4-hydroxymethyl-1 : 3-dithiolan (212 g.) was refluxed with thionyl chloride (145 g.) in benzene (500 c.c.) until no more hydrogen chloride was evolved. The solution was then evaporated, and the residue distilled, at low pressure. Yield, 140 g. of 2-*phenyl*-4-*chloromethyl*-1 : 3-*dithiolan*; b. p. 150°/0·8 mm.; m. p. 69—70° (Found: S, 27·6; Cl, 15·6. $C_{10}H_{11}ClS_2$ requires S, 27·8; Cl, 15·4%). 2-Phenyl-4-chloromethyl-1 : 3-dithiolan (23 g.) was refluxed for 6 hours with potassium cyanide (7·0 g.) and sodium iodide (0·2 g.) in methanol (200 c.c.). The product was worked up in the usual way. Yield, 16 g. of 2-*phenyl*-4-*cyanomethyl*-1 : 3-*dithiolan*; b. p. 180°; m. p. 69° (Found: S, 28·8. $C_{11}H_{11}NS_2$ requires S, 29·1%). 2 : 3-Dimercaptopropanol (124 g.) and acetaldehyde (45 g.) were refluxed for 3 hours in benzene (200 c.c.) with the addition of a few drops of hydrochloric acid as a catalyst. After evaporation of the solvent the residue was distilled at low pressure. Yield, 98 g. of 2-*methyl*-4-*hydroxymethyl*-1 : 3-*dithiolan*; b. p. 115°/0·8 mm.; m. p. 57—58° (Found: S, 42·9. $C_5H_{10}OS_2$ requires S, 42·7%). 2-Methyl-4-hydroxymethyl-1 : 3-dithiolan (30 g.) was converted into 2-*methyl*-4-*chloromethyl*-1 : 3-*dithiolan* by heating with thionyl chloride (22 g.) in benzene (100 c.c.). Yield, 23 g.; b. p. 94°/2·0 mm. (Found: S, 37·7; Cl, 20·8. $C_5H_9ClS_2$ requires

* Analyses by Mr. F. Hall, Dyson Perrins laboratory.

S, 38·0; Cl, 21·1%). Acetone (29 g.) and 2 : 3-dimercaptopropanol (62 g.) were condensed in the usual way to give 2 : 2-*dimethyl*-4-*hydroxymethyl*-1 : 3-*dithiolan* (54 g.) which was crystallised from benzene–light petroleum (b. p. 40—60°); b. p. 105°/1·0 mm.; m. p. 54—55° (Found: S, 39·2. $C_6H_{12}OS_2$ requires 39·0%). 2 : 2-*Dimethyl*-4-*chloromethyl*-1 : 3-*dithiolan* was obtained in 72% yield by the method already described; b. p. 80°/0·7 mm. (Found: S, 35·5; Cl, 19·2. $C_6H_{11}ClS_2$ requires S, 35·1; Cl, 19·4%). 2 : 3-Dimercaptopropanol (124 g.) and *cyclo*hexanone (98 g.) in benzene (200 c.c.) in the same way gave 2 : 2-*pentamethylene*-4-*hydroxymethyl*-1 : 3-*dithiolan* (130 g.); b. p. 150°/0·8 mm.; m. p. 70° (Found: S, 31·7. $C_9H_{16}OS_2$ requires S, 31·4%).

Condensation Products of Dithiols with Dichloroarsines.—The various dithiols and the arsenical compounds were all condensed in the same way. The arsenical compound (0·05 mol.) in chloroform (100 c.c.) was slowly added to a solution of dithiol (0·05 mol.) and pyridine (0·1 mol.) in chloroform (60 c.c.) at 0—5°. The chloroform solution was washed with dilute hydrochloric acid and water, dried (Na_2SO_4), and filtered, and after evaporation of the chloroform the residue was distilled at low pressure. 4-*Hydroxymethyl*-2-(2-*chlorovinyl*)-1 : 3-*dithia*-2-*arsa*cyclo*pentane* (yield, 65%) had b. p. 165°/0·2 mm. (Found: S, 24·6; Cl, 13·8; As, 28·17. $C_5H_8OClS_2As$ requires S, 24·7; Cl, 13·7; As, 29·0%). 2-*Phenyl*-4-*hydroxymethyl*-1 : 3-*dithia*-2-*arsa*cyclo*pentane* was not distilled but crystallised from benzene; yield, 65%; m. p. 97—98° (Found: S, 23·5; As, 27·0. $C_9H_{11}OS_2As$ requires S, 23·3; As, 27·3%). 2-*Methyl*-4-*hydroxymethyl*-1 : 3-*dithia*-2-*arsa*cyclo*pentane* (yield, 70%) had b. p. 158°/1·5 mm. (Found: S, 30·3. $C_4H_8OS_2As$ requires S, 30·2%). 4-*Methyl*-2-(2-*chlorovinyl*)-1 : 3-*dithia*-2-*arsa*cyclo*pentane* (yield 75%) had b. p. 127°/0·6 mm. (Found: S, 26·6; Cl, 14·5; As, 30·7. $C_5H_8ClS_2As$ requires S, 26·4; Cl, 14·6; As, 30·9%). 2-(2-*Chlorovinyl*)-1 : 3-*dithia*-2-*arsa*cyclo*pentane* (yield, 56%) had b. p. 120°/0·4 mm.; on standing it slowly crystallised; m. p. 35° (Found: S, 28·3; Cl, 15·7; As, 33·2. $C_4H_6ClS_2As$ requires S, 28·0; Cl, 15·5; As, 32·8%). 4-*Methoxymethyl*-2-(2-*chlorovinyl*)-1 : 3-*dithia*-2-*arsa*cyclo*pentane* (yield, 78%) had b. p. 145°/0·6 mm. (Found: S, 23·8; Cl, 12·9; As, 27·3. $C_6H_{10}OClS_2As$ requires S, 23·5; Cl, 13·0; As, 27·4%). 5-*Hydroxy*-2-(2-*chlorovinyl*)-1 : 3-*dithia*-2-*arsa*cyclo*hexane* (yield, 65%) had b. p. 160°/0·8 mm. (Found: S, 24·8; Cl, 13·9; As, 29·5. $C_5H_8OClS_2As$ requires S, 24·7; Cl, 13·7; As, 29·0%). 5-*Hydroxy*-2-*phenyl*-1 : 3-*dithia*-2-*arsa*cyclo*hexane* (yield, 60%) had b. p. 190°/1·0 mm. (Found: S, 23·3; As, 27·8. $C_9H_{11}OS_2As$ requires S, 23·3; As, 27·3%). 2-(2-*Chlorovinyl*)-1 : 3-*dithia*-2-*arsa*cyclo*hexane* (yield, 59%) had b. p. 150°/0·4 mm. (Found: S, 26·8; Cl, 14·7; As, 30·8. $C_5H_8ClS_2As$ requires S, 26·4; Cl, 14·6; As, 30·9%). A solution of *p*-carboxyphenyldichloroarsine (26·7 g.) in chloroform (300 c.c.) was added to 2 : 3-dimercaptopropanol (12·4 g.) and pyridine (16 c.c.) in chloroform (100 c.c.). On the addition of 2N-hydrochloric acid to remove pyridine, 2-(p-*carboxyphenyl*)-4-*hydroxymethyl*-1 : 3-*dithia*-2-*arsa*cyclo*pentane* separated. The product was filtered off, and washed with N-hydrochloric acid and finally water; it was then crystallised from ethanol giving 23 g.; m. p. 178—180° (Found: S, 19·6. $C_{10}H_{11}O_3S_2As$ requires S, 20·1%). The *brucine* salt had m. p. 203—206° (decomp.) (Found: S, 9·0. $C_{33}H_{37}O_7N_2S_2As$ requires S, 9·0%).

This work was carried out under the direction of Professor R. A. Peters, M.C., F.R.S., for the Chemical Defence Research Department of the Ministry of Supply. I wish to thank the Director General of Scientific Research (Defence), Ministry of Supply, for permission to publish this work, Dr. V. P. Whittaker for the arsenic estimations, and Messrs. C. Dear and E. Facer for technical assistance.

Department of Biochemistry, Oxford. [*Received, July 19th*, 1946.]

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109. *Synthesis of Diaminoacridines. Part II.*

By Alan A. Goldberg and William Kelly.

1 : 6- and 1 : 9-Diaminoacridines have been synthesised for examination as bacterial inhibitors. Attempts to prepare 4 : 6-diaminoacridine have not been successful.

Of the ten theoretically possible (1—4) : (6—9)-diamino-acridines seven have previously been described, *viz.*, 1 : 7-, 1 : 8-, 2 : 6-, 2 : 7-, 2 : 8-, 3 : 6-, and 3 : 7-diaminoacridines (Benda, *Ber.*, 1912, **45**, 1787; Bogert, Hirschfelder, and Lauffer, *Coll. Trav. Chim., Czeckoslov.*, 1930, **5**—**6**, 382; Lehmstedt and Hundertmark, *Ber.*, 1931, **64**, 2386; Scherlin *et alii*, *Annalen*, 1935, **516**, 218; Albert and Linnell, *J.*, 1936, 89 and 1614; Lehmstedt, *Ber.*, 1937, **70**, 846; Albert, Dyer, and Linnell, *Quart. J. Pharm. Pharmacol.*, 1937, **10**, 649; Albert and Linnell, *J.*, 1938, 22; Goldberg and Kelly, *J.*, 1946, 102). The present communication records the synthesis of 1 : 6- and 1 : 9-diaminoacridines together with attempts to obtain the remaining unknown 4 : 6-isomeride. The compounds were prepared for examination as bacterial inhibitors.

2-Chloro-3-nitrobenzoic acid condensed with *m*-nitroaniline to give 6 : 3′-*dinitrodiphenylamine*-2-*carboxylic acid*, which on treatment with sulphuric acid cyclised to 1 : 6-*dinitroacridone*; reduction of the latter with stannous chloride yielded 1 : 6-*diaminoacridone*, m. p. 320—322°, and this on further reduction with sodium amalgam followed by oxidation was converted into 1 : 6-*diaminoacridine*, m. p. 194—196°. Similarly 2-chloro-3-nitrobenzoic acid condensed with *m*-phenylenediamine to give 6-*nitro*-3′-*aminodiphenylamine*-2-*carboxylic acid*, which with sulphuric acid cyclised to 1-nitro-8-aminoacridone; this by standard methods yielded 1 : 8-diaminoacridone, m. p. 360—362°, and 1 : 8-diaminoacridine, m. p. 248—250° (cf. Albert and Linnell,

J., 1936, 1614, who made this compound from 2-chloro-4-nitrobenzoic acid and *o*-nitroaniline following by cyclisation and reduction). This constitutes an additional example (cf. Part I, *J.*, 1946, 103) of the directional cyclisation of 3'-substituted diphenylamine-2-carboxylic acids, *viz.*, with the 3'-nitro-series *ortho*-closure of the acridone ring prevails, while with the 3'-amino-series *para*-closure predominates.

2-Chloro-3-nitrobenzoic acid condensed with *o*-nitroaniline to give 6 : 2'-*dinitrodiphenylamine-2-carboxylic acid*, which by similar methods was converted into 1 : 9-*dinitroacridone*, 1 : 9-*diaminoacridone*, and 1 : 9-*diaminoacridine*.

2-Chloro-6-nitrobenzoic acid failed to condense with *m*-nitroaniline, both reactants being recovered under all the experimental conditions employed; this accords with the failure of 2-chloro-6-nitrobenzoic acid to condense with aniline (Tuttle, *J. Amer. Chem. Soc.*, 1923, **45**, 1916) and the failure of 6-nitro-2-aminobenzoic acid to condense with *o*-chloronitrobenzene (Bogert *et al.*, *loc. cit.*). On the other hand 2-chloro-6-acetamidobenzoic acid readily condensed with *m*-nitroaniline to yield 3'-*nitro*-3-*acetamidodiphenylamine-2-carboxylic acid*, but this compound could not be induced to cyclise into the desired acridone on treatment with sulphuric acid, phosphoryl chloride, phosphoric acid, fused boric acid, thionyl chloride, or stannic chloride (cf. the inability of 3-nitrodiphenylamine-2-carboxylic acid to cyclise to 4-nitroacridone, Lehmstedt and Schrader, *Ber.*, 1937, **70**, 1528).

The antibacterial properties of 1 : 6- and 1 : 9-diaminoacridines will be reported shortly.

Experimental.

The Ullmann condensations were normally carried out by the same method as that described previously.

6 : 3'-*Dinitrodiphenylamine-2-carboxylic Acid.*—2-Chloro-3-nitrobenzoic acid (10 g.), *m*-nitroaniline (8 g.), potassium carbonate (8 g.), and copper powder (0·2 g.) were melted together and kept at 180° for 5 hours. The resulting product was boiled with water (200 c.c.), the insoluble material removed, and the hot solution acidified with 5N-hydrochloric acid. The precipitate was collected and recrystallised from aqueous alcohol, the *acid* being obtained in yellow prisms (7·5 g.), m. p. 196—198° (Found: N, 13·9; *M* (titration), 298. $C_{13}H_9O_6N_3$ requires N, 13·9%; *M*, 303).

1 : 6-*Dinitroacridone.*—A solution of the foregoing acid (13 g.) in sulphuric acid (91 c.c.) was heated at 90° for ½ hour, cooled, and poured on excess of crushed ice. The precipitate was filtered off, and stirred with dilute ammonia, and the insoluble 1 : 6-dinitroacridone collected, washed with water, and dried (12 g.; m. p. 324—328°). Recrystallisation of a sample from aqueous pyridine gave the pure *compound* in yellow needles, m. p. 332—334° with softening at 320° (Found: N, 14·9. $C_{13}H_7O_5N_3$ requires N, 14·7%).

1 : 6-*Diaminoacridone.*—Crude 1 : 6-dinitroacridone (12 g.) was stirred with a solution of stannous chloride crystals (120 g.) in 10N-hydrochloric acid (120 c.c.) at 100° for 1 hour. The resulting liquid was cooled, the precipitate of the stannichloride complex collected and stirred with N-sodium hydroxide (300 c.c.) for ½ hour, and the insoluble diaminoacridone (9 g.; m. p. 312°) collected and washed. Recrystallisation from aqueous pyridine gave 1 : 6-*diaminoacridone* in felted yellow needles, m. p. 320—322° depressed by admixture with 1 : 8-diaminoacridone obtained by cyclisation of 6-nitro-3'-aminodiphenylamine-2-carboxylic acid followed by reduction (Found: C, 69·2; H, 5·0; N, 18·7. $C_{13}H_{11}ON_3$ requires C, 69·3; H, 4·9; N, 18·7%).

1 : 6-*Diaminoacridine.*—A suspension of crude 1 : 6-diaminoacridone (5·0 g.) in 60% ethyl alcohol (400 c.c.) was saturated with carbon dioxide and stirred with sodium amalgam (4%; 200 g.) for 1 hour at 20° and then for a further 1 hour at 60°, the stream of carbon dioxide being maintained throughout. Ferric chloride solution (10%; 5 c.c.) was added and a current of air passed into the rapidly stirred suspension at 60° for 1½ hours. The filtered solution was evaporated to small volume and allowed to stand. 1 : 6-Diaminoacridine separated in dark brown prisms (3·0 g.; m. p. 188—190°). Recrystallisation from aqueous alcohol gave the pure *compound* in orange brown needles, m. p. 194—196° (Found: C, 74·2; H, 5·4; N, 20·4. $C_{13}H_{11}O_3$ requires C, 74·6; H, 5·3; N, 20·1%). The hydrochloride is easily soluble in cold water.

6-*Nitro*-3'-*aminodiphenylamine-2-carboxylic Acid.*—2-Chloro-3-nitrobenzoic acid (6·7 g.), *m*-phenylenediamine (5·4 g.), potassium carbonate (5·0 g.), copper powder (0·2 g.), and amyl alcohol (30 c.c.) were heated at 120—125° (bath temp.) for 2 hours and the product isolated in the manner formerly described. The crude amino-acid (5·3 g.) had m. p. 240—280° (slow decomposition) and could not be purified by crystallisation. Acetylation by the method previously used (Goldberg and Kelly, *J.*, 1946, 107) yielded 6-*nitro*-3'-*acetamidodiphenylamine-2-carboxylic acid* which separated from aqueous alcohol in vermilion needles, m. p. 226—228° (Found: C, 56·8; H, 4·2; N, 13·2. $C_{15}H_{13}O_6N_3$ requires C, 57·1; H, 4·1; N, 13·3%).

1-*Nitro*-8-*aminoacridone.*—Crude 6-nitro-3'-amino-diphenylamine-2-carboxylic acid (3·1 g.) was dissolved in sulphuric acid (22 c.c.), and the solution heated to 90—95° for ½ hour and poured on powdered ice. The mixture was basified with ammonia and the crude 1-nitro-8-aminoacridone (2·5 g.; m. p. 304—306°) collected; recrystallisation from aqueous pyridine gave the pure *compound* in purple brown needles, m. p. 314—316° (Found: N, 16·4. $C_{13}H_9O_3N_3$ requires N, 16·5%).

1 : 8-*Diaminoacridone.*—Crude 1-nitro-8-aminoacridone (2·0 g.) was heated with a solution of stannous chloride crystals (20 g.) in concentrated hydrochloric acid (20 c.c.) for 1 hour at 100°, the solution cooled, and the precipitate of the stannichloride complex collected. This was dissolved in water, excess of cold 5N-sodium hydroxide solution added, and the precipitate (1·1 g.; m. p. 356—358°) collected and washed

with water; recrystallisation from aqueous pyridine gave 1 : 8-diaminoacridone in golden brown needles, m. p. 360—362° (Albert and Linnell, *J.*, 1936, 1614 record m. p. >360° for 1 : 8-diaminoacridone prepared by a different synthetic method) (Found : C, 69·0; H, 5·1; N, 18·6. Calc. for $C_{13}H_{11}ON_3$: C, 69·3; H, 4·9; N, 18·7%).

1 : 8-*Diaminoacridine.*—Reduction of the foregoing diaminoacridone by the same method as described for the 1 : 6-isomeride yielded 1 : 8-diaminoacridine in 65% yield; it crystallised from alcohol in felted orange needles, m. p. 248—250° (Found : N, 20·3. Calc. for $C_{13}H_{11}N_3$: N, 20·1%).

6 : 2′-*Dinitrodiphenylamine-2-carboxylic Acid.*—2-Chloro-3-nitrobenzoic acid (10 g.), *o*-nitroaniline (8 g.), potassium carbonate (8 g.), copper powder (0·2 g.), and amyl alcohol (20 c.c.) were heated to 180° (internal) for 5 hours, the solvent being allowed to distil slowly. The *acid* isolated in the usual manner crystallised from aqueous alcohol in golden yellow needles (3·6 g.), m. p. 252—254° (Found : C, 51·6; H, 3·0; N, 13·9. $C_{13}H_8O_8N_3$ requires C, 51·5; H, 3·0; N, 13·9%).

1 : 9-*Dinitroacridone.*—The foregoing acid (11 g.) cyclised in the same manner as described for the 1 : 6-isomeride yielded crude 1 : 9-dinitroacridone, m. p. 264—266°, as a yellow powder (9·6 g.). Recrystallisation of a sample from aqueous pyridine gave the pure *compound* in slender yellow needles, m. p. 266—268° (Found : C, 54·9; H, 2·3; N, 14·9. $C_{13}H_7O_5N_3$ requires C, 54·7; H, 2·5; N, 14·7%).

1 : 9-*Diaminoacridone.*—1 : 9-Dinitroacridone (13 g.) was heated with a solution of stannous chloride crystals (130 g.) in concentrated hydrochloric acid (130 c.c.) at 100° for 3 hours. The product was treated in the usual manner and yielded crude 1 : 9-diaminoacridone (10 g.; m. p. 330°) as a yellow powder which crystallised from dilute pyridine in olive green needles, m. p. 340—342° (Found : C, 69·2; H, 5·0; N, 18·7. $C_{13}H_{11}ON_3$ requires C, 69·2; H, 4·9; N, 18·7%). The hydrochloride is almost insoluble in water while the free diamine is easily soluble in dilute sodium hydroxide.

1 : 9-*Diaminoacridine.*—A suspension of 1 : 9-diaminoacridone (5·0 g.) in 60% alcohol was stirred with 4% sodium amalgam (220 g.) for 2 hours at 20° and then for a further 1 hour at 60°; during the whole time the suspension was kept saturated with carbon dioxide. Ferric chloride (10%; 5 c.c.) was added and a current of air beaten into the rapidly stirred suspension at 60° for 2 hours. Boiling alcohol (200 c.c.) was added, the liquid filtered hot, and the filtrate evaporated to small volume and allowed to cool; 1 : 9-diaminoacridine separated in brown needles (3·9 g.), m. p. 180—182°. Recrystallisation from dilute alcohol gave the pure *compound* in orange brown needles, m. p. 182° (Found : C, 73·8; H, 5·1; N, 20·1. $C_{13}H_{11}N_3$ requires C, 74·6; H, 5·3; N, 20·1%). The hydrochloride dissolves easily in cold water.

3′-*Nitro*-3-*acetamidodiphenylamine*-2-*carboxylic Acid.*—2-Chloro-6-acetamidobenzoic acid (30 g.), *m*-nitroaniline (24 g.), potassium carbonate (21 g.), and copper powder (0·5 g.) were heated with *cyclo*hexanol (80 c.c.) at 190° (bath temp.) for 4 hours. The crude acid was isolated in the normal manner, extracted with boiling water (3 × 500 c.c.), the residual insoluble acid dissolved in N-sodium hydroxide solution (200 c.c.), and the sodium salt precipitated by the addition of saturated sodium chloride solution (200 c.c.). The salt was collected, washed with cold brine, and dissolved in water, and the filtered solution acidified with hydrochloric acid; the crude precipitated acid (19 g.) was collected and recrystallised from aqueous alcohol, 3′-*nitro*-3-*acetamidodiphenylamine*-2-*carboxylic acid* separating in yellow needles, m. p. 182—184° (Found : N, 13·6; *M* (titration), 320. $C_{15}H_{13}O_5N_3$ requires N, 13·4%; *M*, 315).

Attempted Cyclodehydration of 3′-*Nitro*-3-*acetamidodiphenylamine*-2-*carboxylic Acid.*—The foregoing acid (6·1 g.) was heated with sulphuric acid (43 c.c.) at 100° for 1½ hours, the solution cooled, water (25 c.c.) added, and the heating at 100° continued for ½ hour. Basification with ammonia yielded a brown gum which was purified by dissolution in dilute hydrochloric acid (charcoal) and reprecipitation with ammonia. Recrystallisation of this from aqueous methyl alcohol yielded 3-*nitro*-3′-*aminodiphenylamine* (1·7 g.) in scarlet needles, m. p. 120—122° (Found : C, 62·6; H, 5·0; N, 18·5. $C_{13}H_{11}O_2N_3$ requires C, 62·8; H, 4·8; N, 18·2%). The same diphenylamine was obtained when attempts were made to effect cyclisation with phosphoric acid. With phosphorus pentachloride–aluminium chloride, thionyl chloride–aluminium chloride, fused boric acid, or stannic chloride no nitro-amino-acridone could be isolated; either the original compound was recovered or else the nitro-amino-diphenylamine was obtained by loss of carbon dioxide.

WARD, BLENKINSOP & CO. LTD.,
RESEARCH LABORATORIES, BRADFORD-ON-AVON.

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110. *Composition, Pressure, and Temperature Relationships in Binary Azeotropic Systems.*

By E. A. COULSON and E. F. G. HERINGTON.

Equations previously derived on thermodynamic grounds for expression of the change of composition in binary azeotropes with temperature and pressure are re-examined and developed. The exact thermodynamic relationships are of little practical utility unless supplemented with an equation of state in some form.

Using an approximate statistical thermodynamical treatment, it is shown that azeotropes formed in " strictly regular solutions " (as defined by Guggenheim and Fowler) would obey the empirical rules of azeotropic behaviour, and it is therefore suggested that many real azeotropes closely conform to these " regular or normal " azeotropes.

This leads to the development of general equations relating azeotropic composition to temperature and pressure and other determinable quantities. Comparison of calculated with

experimental data shows that the equations fit the experimental results very closely in some instances.

The semi-empirical methods used by Kireev and by Carlson and Colburn for calculation of azeotropic composition are examined, and it is concluded that no better agreement between theory and experiment was obtained than is afforded by the statistical thermodynamical approximate treatment.

Although azeotropes formed in normal liquids should, and do, conform closest to the requirements of the present treatment, it also appears that the general relationships retain some validity even if the components are abnormal (*i.e.*, are associated or solvated).

In recent years a considerable extension of the use of azeotropes in fractional distillation practice has been made and it is now recognised that azeotrope formation is of common occurrence and may often be turned to advantage in devising separation processes. The variations of the azeotropic composition with boiling point and distillation pressure are of obvious practical importance. A fresh interest is thus lent to such theoretical conclusions regarding these properties of constant-boiling mixtures as thermodynamical or statistical reasoning will afford. In the present discussion, restricted to binary systems, our object has been to trace out as directly as possible the general relationship between the variables and to extract useful approximate equations which can be applied to experimental results. These equations have been tested on one or two well-studied examples where very reliable experimental data are available. That the treatment now offered is based on a critical re-examination of the diverse methods previous workers had adopted in approaching the problems will be apparent from the form in which it is developed.

The systems we consider have two components and two phases (liquid, vapour) in equilibrium, the total pressure being that of the vapour phase. Hence by the phase rule in the unrestricted case there are two degrees of freedom; *i.e.*, if the liquid composition and the temperature be fixed then the composition of the vapour and its total pressure are also determined. It will be assumed that the laws of ideal gases apply to the vapour phase and, therefore, that the partial pressures of the two components are proportional to the respective mol.-fractions. When azeotropism occurs in such systems it is defined by the condition that the liquid boils unchanged, *i.e.*, the compositions of vapour and liquid expressed in mol.-fractions are identical. Hence $p_1/P = N_1$ and $p_2/P = N_2$, and moreover, the volatility ratio α $(= p_1N_2/p_2N_1)$ equals 1 (p_1 and p_2 are the partial pressures of components 1 and 2 in equilibrium at total pressure P with a solution containing N_1 mols. of component 1 and N_2 mols. of component 2). Other related criteria are that a maximum or minimum in the curve connecting boiling point at constant pressure with liquid composition occurs at an azeotropic composition, and so also does a minimum or maximum in the curve of total pressure when, at constant temperature, pressure is plotted against liquid composition. The variation of the composition of an azeotrope with pressure and boiling point was originally taken as evidence for the view that azeotropes are not chemical compounds.

A deduction previously given by Redlich and Schutz (*J. Amer. Chem. Soc.*, 1944, **66**, 1007) of the formal thermodynamic relationships between these variations of pressure, composition, and boiling point in azeotropic systems requires modification, and the complete derivation of the necessary equations will therefore be presented. The phase rule indicates that binary two-phase systems possess two degrees of freedom. To deduce the relation between pressure and temperature, we take T (the temperature) and N_2 as variables and write $P = \mathrm{f}(N_2,T)$ and hence

$$\frac{\mathrm{d}P}{\mathrm{d}T} = \left(\frac{\partial P}{\partial T}\right)_{N_2} + \left(\frac{\partial P}{\partial N_2}\right)_T \cdot \frac{\mathrm{d}N_2}{\mathrm{d}T} \quad \ldots\ldots\ldots\ldots \quad (1)$$

For an azeotrope $(\partial P/\partial N_2)_T = 0$, since this implies a maximum or minimum in the P–N_2 curve at constant T, and hence

$$\left(\frac{\mathrm{d}P}{\mathrm{d}T}\right)_{\mathrm{az.}} = \left(\frac{\partial P}{\partial T}\right)_{N_2} \quad \ldots\ldots\ldots\ldots \quad (2)$$

The subscript az. indicates that equation (2) refers to the azeotrope. But $\partial P = \partial p_1 + \partial p_2$, hence from (2)

$$\frac{1}{P}\left(\frac{\mathrm{d}P}{\mathrm{d}T}\right)_{\mathrm{az.}} = \frac{1}{P}\left(\frac{\partial p_1}{\partial T}\right)_{N_2} + \frac{1}{P}\left(\frac{\partial p_2}{\partial T}\right)_{N_2}$$

or

$$T^2\left(\frac{\mathrm{d}\ln P}{\mathrm{d}T}\right) = T^2\frac{p_1}{P}\left(\frac{\partial \ln p_1}{\partial T}\right)_{N_2} + T^2\frac{p_2}{P}\left(\frac{\partial \ln p_2}{\partial T}\right)_{N_2}$$

and since for the azeotrope $p_1/P = N_1$, $p_2/P = N_2$, and $N_1 = 1 - N_2$, and since in general

$$T^2(\partial \ln p/\partial T)_N = \bar{H}/R$$

where $\bar{H}$ is the partial molal heat of vaporisation of a component from solution, we obtain after substitution and rearrangement

$$\left[\frac{\mathrm{d}\ln P}{\mathrm{d}(1/T)}\right]_{az.} = -\frac{(1-N_2)\bar{H}_1 + N_2\bar{H}_2}{R} \quad \ldots\ldots\ldots \quad (3)$$

Equation (3) connects the variation in azeotropic pressure with the reciprocal of azeotropic boiling point and the composition and heat quantities shown on the right. When T changes, N_2 alters, and $\bar{H}_1$ and $\bar{H}_2$, besides being temperature dependent, also depend upon the composition, being defined by

$$\bar{H}_1 = (\partial H/\partial n_1)_{T,n_2} \quad \text{and} \quad \bar{H}_2 = (\partial H/\partial n_2)_{T,n_1}$$

where H is the latent heat of vaporisation of a solution containing n_1 and n_2 mols. of the respective components. While, therefore, (3) has the form of the Clausius–Clapeyron equation, it has no practical utility except when the numerator on the right can be treated as constant over temperature and composition ranges.

To derive the variation of azeotropic composition with temperature we choose T and N_2 as the two independent variables, in accordance with the phase-rule requirement for any binary two-phase system, and write the volatility ratio $\alpha = f(T,N_2)$ and hence

$$\frac{\mathrm{d}\alpha}{\mathrm{d}T} = \left(\frac{\partial\alpha}{\partial T}\right)_{N_2} + \left(\frac{\partial\alpha}{\partial N_2}\right)_T \cdot \frac{\mathrm{d}N_2}{\mathrm{d}T} \quad \ldots\ldots\ldots \quad (4)$$

For an azeotropic system $\alpha = 1$, thus $\alpha =$ constant and $\mathrm{d}\alpha/\mathrm{d}T = 0$, hence from (4)

$$\left(\frac{\mathrm{d}N_2}{\mathrm{d}T}\right)_{az.} = \left(\frac{\mathrm{d}N_2}{\mathrm{d}T}\right)_{\alpha=1} = -\frac{\left(\frac{\partial\alpha}{\partial T}\right)_{N_2}}{\left(\frac{\partial\alpha}{\partial N_2}\right)_T} \quad \ldots\ldots\ldots \quad (5)$$

Equation (5) connects the variation in azeotropic composition and boiling point with partial derivatives of α at points where $\alpha = 1$. It differs from the expression given by Redlich and Schutz (*loc. cit.*), who assumed α could be a function of *three* independent variables.

The right-hand side of (5) may be developed as follows :

$$\begin{aligned}\left(\frac{\partial\alpha}{\partial T}\right)_{N_2} &= \alpha\left(\frac{\partial\ln\alpha}{\partial T}\right)_{N_2} \\ &= \alpha\left[\frac{\partial(\ln p_1 + \ln N_2 - \ln p_2 - \ln N_1)}{\partial T}\right]_{N_2} \\ &= \alpha\left(\frac{\partial\ln p_1/p_2}{\partial T}\right)_{N_2} \quad \ldots\ldots\ldots \quad (6) \\ \left(\frac{\partial\alpha}{\partial N_2}\right)_T &= \alpha\left(\frac{\partial\ln\alpha}{\partial N_2}\right)_T \\ &= \alpha\left[\frac{\partial\ln p_1/N_1}{\partial N_2} - \frac{\partial\ln p_2/N_2}{\partial N_2}\right]_T\end{aligned}$$

The Duhem–Margules equation in the form $N_1 . \partial\ln p_1/N_1 + N_2 . \partial\ln p_2/N_2 = 0$ (here $N_1 + N_2 = 1$) is combined with the foregoing to yield

$$\left(\frac{\partial\alpha}{\partial N_2}\right)_T = -\frac{\alpha}{1-N_2}\cdot\left(\frac{\partial\ln p_2/N_2}{\partial N_2}\right)_T \quad \ldots\ldots\ldots \quad (7)$$

and from (5), (6), and (7) we obtain

$$\left(\frac{\mathrm{d}N_2}{\mathrm{d}T}\right)_{\alpha=1} = \frac{(1-N_2)\left(\frac{\partial\ln p_1/p_2}{\partial T}\right)_{N_2}}{\left(\frac{\partial\ln p_2/N_2}{\partial N_2}\right)_T} \quad \ldots\ldots\ldots \quad (8)$$

in which the second term of the numerator may be replaced by $(\bar{H}_1 - \bar{H}_2)/RT^2$ but it must be remembered that in the general case $\bar{H}_1$ and $\bar{H}_2$ are functions of N_2, *i.e.*, of T.

The combination of (8) with (3) can be made in order to derive the change of composition with pressure.

Clearly, equation (8), like (3), is of little practical utility, since the right-hand terms are more

difficult to measure than those on the left and the explicit functional relationship between N_2 and T cannot be determined without integration.

Kireev (*Acta Physicochim., U.S.S.R.*, 1941, **14**, 371) sought to elucidate the general relationship between azeotropic compositions, pressures, and temperatures and the properties of the pure components by a somewhat different approach but one based nevertheless on thermodynamical reasoning. As his mathematical derivations are difficult to interpret and are obscured by a number of printer's errors they will be developed directly in the nomenclature used earlier in this paper. The free energy of formation from the pure components of any binary liquid mixture may be written

$$\Delta G = -RT\,(N_1 \ln p_1^\circ/p_1 + N_2 \ln p_2^\circ/p_2)$$

where p_1° and p_2° are the vapour pressures of the two pure components. For a hypothetical ideal mixture of the same composition, $p_1 = N_1 p_1^\circ$ and $p_2 = N_2 p_2^\circ$, so that in this case the free energy

$$\Delta G^i = -RT(N_1 \ln 1/N_1 + N_2 \ln 1/N_2)$$

The difference between ΔG and ΔG^i is defined as the " excess free energy " ΔG^E, and clearly

$$\Delta G^E = RT\,(N_1 \ln p_1/N_1 p_1^\circ + N_2 \ln p_2/N_2 p_2^\circ) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Differentiation with respect to N_2 at constant T, and remembering that $N_1 = 1 - N_2$, gives

$$\left(\frac{\partial \Delta G^E}{\partial N_2}\right)_T = RT\left[-\ln \frac{p_1}{N_1 p_1^\circ} + (1 - N_2).\left(\frac{\partial \ln p_1}{\partial N_2} + \frac{1}{1 - N_2}\right)\right] + RT\left[\ln \frac{p_2}{N_2 p_2^\circ} + N_2.\left(\frac{\partial \ln p_2}{\partial N_2} - \frac{1}{N_2}\right)\right]$$

$$= RT\left[\ln \frac{p_1^\circ}{p_2^\circ} + \ln \frac{p_2}{N_2}\frac{N_1}{p_1} + (1 - N_2)\frac{\partial \ln p_1}{\partial N_2} + N_2 \frac{\partial \ln p_2}{\partial N_2}\right]$$

$$= RT\left[\ln \frac{p_1^\circ}{p_2^\circ} + \ln \frac{p_2}{N_2}\frac{N_1}{p_1}\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

The last simplification is obtained by using the Duhem–Margules relationship. Equation (10) is true for any binary liquid mixture. For an azeotrope the second term on the right is zero so that

$$(\partial \Delta G^E/\partial N_2)_T = RT \ln p_1^\circ/p_2^\circ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

It should be noted that (11) is true only for $\alpha = 1$, and this applies only to the azeotropic condition in contrast with equations (5) and (8) which hold for any constant values of α. Clearly also (11) can only be used to obtain a relationship between azeotropic composition and temperature if a functional relationship between ΔG^E, N_2, and T can be found.

It will now be seen that the strictly thermodynamic approach has not proved very profitable, and that a less rigorous treatment may well afford a more practically useful basis for discussing quantitatively the occurrence and behaviour of azeotropes.

An Approximate Treatment based on Statistical Thermodynamical Considerations.—It has been usual to compare the properties of solutions with the assumed properties of hypothetical ideal solutions and to measure deviations from ideal behaviour. Ideal solutions cannot form azeotropes and therefore are unsuitable in many ways for introduction into the discussion of azeotropy. We suggest that " strictly regular solutions " as defined by Guggenheim and Fowler (" Statistical Thermodynamics ", p. 351) are a suitable class of solutions to be regarded as capable under certain conditions of yielding what we may call " normal or regular " azeotropes. We shall show that certain real azeotropic mixtures closely conform in behaviour with the azeotropes to which strictly regular solutions may be expected to give rise.

The conditions for the formation of a strictly regular solution are: (1) The components should pack in the same way. (2) The molar volumes should be sufficiently alike so that a mixture of the two kinds can also pack in the same way as each of the single liquids. (3) The ratio of the free volumes of the two pure liquids should not differ from unity by more than approximately 30%. (4) The molar volumes (V_1, V_2) and free volumes of both components should remain unaltered when the liquids are mixed. (5) In any given configuration of volume V given by $V = N_1V_1 + N_2V_2$ the potential energy W may be regarded as the sum of contributions from pairs of closest neighbours.

A crude statistical thermodynamical treatment of strictly regular solutions which assumes that the entropy of mixing of such a solution is the same as that of an ideal solution yields equations of the form

$$p_1 = p_1^\circ N_1 e^{WabN_1^2/RT} \text{ and } p_2 = p_2^\circ N_2 e^{WabN_1^2/RT} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

where p_1, p_2, p_1°, p_2°, N_1, and N_2 have the same significance as before and Wab is the mixing energy (Guggenheim and Fowler, *op. cit.*). For such a mixture

$$H^1 = [N_1N_2/(N_1 + N_2)]Wab \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

where H^1 is the excess heat over that of an ideal solution. For an ideal solution $H^1 = 0$, $Wab = 0$, and equations (12) reduce to Raoult's equation.

The more refined treatment of strictly regular solutions (Guggenheim and Fowler, *op. cit.*, p. 358) indicates that equations (12) are a good first approximation to the fuller treatment (see also Kirkwood, *J. Physical Chem.*, 1939, **43**, 97, who arrives at a similar conclusion) and they will be taken therefore as the basis for our discussion of azeotropism. We note first that these equations are of the same form as the Margules equation as derived by Porter (*Trans. Faraday Soc.*, 1920, **16**, 336), where $Wab/RT = \beta$, a constant, since the Porter equation applies at constant temperature. The Porter equation is known to correlate fairly accurately the partial pressure of a component and the liquid composition (at constant temperature) except when one or other component is highly associated (see, *e.g.*, Glasstone, " Textbook of Physical Chemistry ", 1940, p. 699).

The application of a set of equations such as (12) to describe the behaviour of an azeotropic system is simply made. The equations are written in the form $p_1 = p_1^\circ N_1\gamma_1$ and $p_2 = p_2^\circ N_2\gamma_2$, where γ_1 and γ_2 are the activity coefficients of the components. For an azeotrope, $p_1N_2/p_2N_1 = 1$, and hence

$$\ln p_1^\circ/p_2^\circ + \ln \gamma_1/\gamma_2 = 0$$

For the particular case under consideration $\gamma_1 = e^{WabN_2^2/RT}$ and $\gamma_2 = e^{WabN_1^2/RT}$, so after substitution and rearrangement we obtain, remembering that $N_1 + N_2 = 1$,

$$N_2(\text{az.}) = \tfrac{1}{2}(1 - RT/Wab \,.\, \ln p_1^\circ/p_2^\circ) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

A number of conclusions can be drawn from equation (14).

Conditions for the existence of an azeotrope. For an azeotrope to have existence, N_2(az.) in equation (14) must lie between 0 and 1, *i.e.*

$$\ln p_1^\circ/p_2^\circ < Wab/RT \quad \text{and} \quad \ln p_2^\circ/p_1^\circ < Wab/RT$$

Since Wab is in general not large, $|p_1^\circ - p_2^\circ|$ must be small for an azeotrope to be formed. This is the physical basis of the empirical rule given by Timmermans (" Les Solutions Concentrées ", 1936, p. 161), *viz.*, that azeotropy is greatly favoured when the pure components are a close-boiling pair.

Maximum and minimum azeotropes. The sign of Wab, in equation (12), determines whether deviations from ideality are positive or negative. If Wab is positive in sign we have positive deviations, and if an azeotrope is formed we have maxima in curves of pressure–composition (at constant temperature) and minima in curves of b. p.–composition (at constant pressure). On the other hand, if Wab is negative the above maxima and minima are interchanged. The only factor which tends to make Wab negative is compound formation between the components, *e.g.*, solvation of hydrogen chloride by water; thus in a maximum b. p. azeotrope this effect must outweigh those factors which operate in the reverse sense, namely, differences between the internal pressure, polarity, molecular size, or degree of association of the components in the liquid state. Thus maximum b. p. azeotropes occur far less commonly than the opposite type.

Direction of change of azeotropic composition with temperature. In the statistical thermodynamical derivation of equation (12) it is assumed that Wab is invariant with temperature, an assumption considered by Guggenheim and Fowler (*op. cit.*) to be a close approximation to reality. We will therefore take Wab as independent of temperature, and hence by differentiating equation (14) with respect to T,

$$\frac{dN_2}{dT} = -\tfrac{1}{2}R/Wab\left[\ln p_1^\circ/p_2^\circ + T \,.\, \frac{d \ln p_1^\circ/p_2^\circ}{dT}\right] . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

Clearly the sign of dN_2/dT depends upon the sign of Wab, so that *ceteris paribus* the variation of concentration with temperature for maximum b. p. azeotropes will be in the reverse sense to that of the minimum b. p. type.

We next consider the terms in the bracket in equation (15). It has already been shown that for most azeotropes $|p_1^\circ - p_2^\circ|$ must be small and hence $\ln p_1^\circ/p_2^\circ \sim 0$, so that the sign of the bracketed quantity is determined by the second term, which is usually numerically the larger. This second term can be expanded in two alternative forms, which will be considered separately.

(1) By using the Clausius–Clapeyron equation we may write

$$T\frac{\mathrm{d}\ln p_1^\circ/p_2^\circ}{\mathrm{d}T} = \frac{H_1 - H_2}{RT}$$

where H_1 and H_2 are the latent heats of vaporisation of the pure components 1 and 2. For a minimum b. p. azeotrope Wab is positive, so that $-\frac{1}{2}R/Wab$ is negative. Hence if $H_2 > H_1$ then the right-hand side of equation (15) is positive, and a rise in temperature will cause an increase in the concentration of the component with the higher latent heat of vaporisation in the pure state.

Since Wab is negative for a maximum b. p. azeotrope, the converse conclusions result for this type by similar reasoning.

These rules are identical with the form of Wrewsky's empirical rule as usually quoted (see, *e.g.*, Young, " Distillation Principles and Processes," p. 61).

(2) Alternatively we may write

$$T\frac{\mathrm{d}\ln p_1^\circ/p_2^\circ}{\mathrm{d}T} = T\left[\frac{1}{p_1^\circ}\frac{\mathrm{d}p_1^\circ}{\mathrm{d}T} - \frac{1}{p_2^\circ}\frac{\mathrm{d}p_2^\circ}{\mathrm{d}T}\right]$$

$$\sim \frac{T}{p_1^\circ}\left[\frac{\mathrm{d}p_1^\circ}{\mathrm{d}T} - \frac{\mathrm{d}p_2^\circ}{\mathrm{d}T}\right]$$

The approximation is justified because in general $|p_1^\circ - p_2^\circ|$ is small. If $\mathrm{d}p_1^\circ/\mathrm{d}T > \mathrm{d}p_2^\circ/\mathrm{d}T$ then the sign of the bracketed quantity in equation (15) is positive, and $\mathrm{d}N_2/\mathrm{d}T$ will be negative, *i.e.*, the azeotropic composition moves towards that component which has the lower $\mathrm{d}p^\circ/\mathrm{d}T$ (in the pure state) as temperature decreases. This is equivalent to the statement that the percentage of that component in a binary azeotropic mixture which has the lower value of $\mathrm{d}p^\circ/\mathrm{d}T$ increases as the pressure decreases, which is the rule arrived at empirically by Merriman (quoted by Young, *op. cit.*, p. 61).

We thus see that Merriman's and Wrewsky's rules may be given an identical basis. Our consideration of strictly regular solutions has shown that the properties derived for the azeotropes which they form accord closely with the behaviour of real azeotropes as expressed in empirical generalisations. This lends support to the suggestion that normal or regular azeotropes should be considered as a class of strictly regular solutions.

Approximate relation between azeotropic composition and boiling point. We now examine equation (14) with the aim of seeing how far simple approximate quantitative expressions derivable from it fit actual data recorded for real azeotropes.

The simple integrated form of the Clausius–Clapeyron equation yields for the pure components

$$\ln p_1^\circ = -H_1/RT + C_1 \quad \text{and} \quad \ln p_2^\circ = -H_2/RT + C_2$$

where C_1 and C_2 are constants. Insertion of these relationships in (14) and rearrangement yields

$$N_2 = \tfrac{1}{2}\left[1 + \frac{H_1 - H_2}{Wab} + \frac{CR}{Wab}T\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

where $C = C_1 - C_2$.

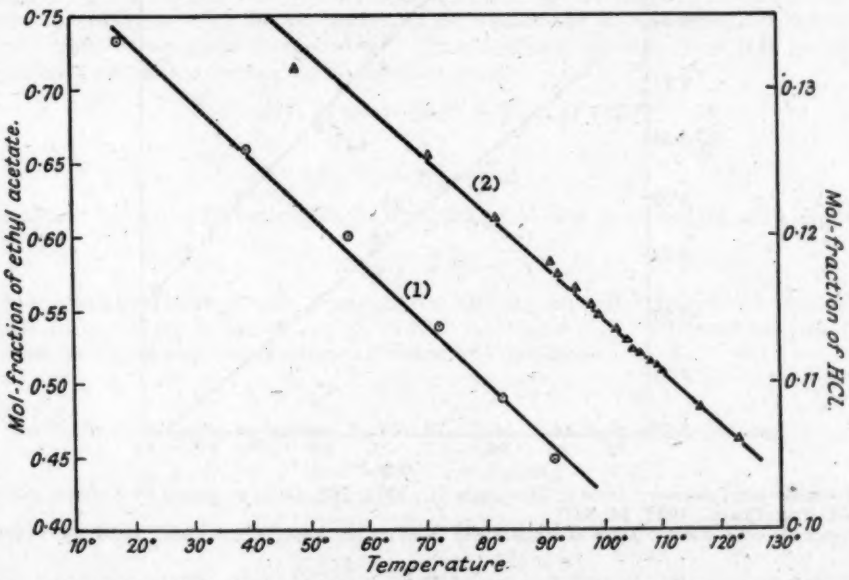
Equation (16) clearly indicates a direct linear relation between the mol.-fraction N_2 and the azeotropic b. p., T. Naturally, a similar relation exists for N_1 and T, since the components are not distinguished in any way.

Reference to plots of experimental data for the azeotropic systems benzene–*cyclo*hexane and ethyl acetate–carbon tetrachloride shows that in these cases where the solutions approach strict regularity a straight-line relation is obeyed (Redlich and Schutz, *loc. cit.*). However, several other examples show the same behaviour although it is improbable that these can be classified as strictly regular (ethyl alcohol–chloroform, methyl alcohol–methyl acetate, heptane–ethyl alcohol, toluene–ethyl alcohol; see Redlich and Schutz, *loc. cit.*). Such plots may clearly be useful even for systems in which one of the components is associated, *e.g.*, ethyl alcohol–ethyl acetate; but they will not serve to correlate the data on the system water–ethyl alcohol, which is known to be very irregular—here the heat of mixing depends markedly on the temperature. Similar experimental data for the well-studied systems ethyl alcohol–ethyl acetate and hydrogen chloride–water (Merriman, *J.*, 1913, **103**, 1801; Bonner and Wallace, *J. Amer. Chem. Soc.*, 1930, **52**, 1747) are plotted in Fig. 1.

The extrapolation of such plots of N_2 against T to $N_2 = 0$ and $N_1 = 1$ permits the temperatures to be found at which azeotropes cease to exist, but is of course subject to the condition that the latent heats H_1 and H_2 and Wab remain constant and independent of

temperature. The upper temperature may be above the critical temperature, or in its vicinity, and the lower temperature below the freezing point of one of the components. In addition, minimum b. p. azeotropes may separate into a two-phase liquid system as the temperature is lowered; this occurs when $Wab/RT > 2$ (for detailed discussion see Guggenheim and Fowler, *loc. cit.*, and Kirkwood, *loc. cit.*). Hence in practice there may not be an upper or lower temperature limit for the azeotropy, although in some cases both or either may exist.

FIG. 1.



(1) *Ethyl acetate–ethyl alcohol: Data of Merriman as quoted by Carlson and Colburn* (Ind. Eng. Chem., 1942, **34**, 581).
(2) *Hydrogen chloride–water: Data of Bonner and Wallace* (J. Amer. Chem. Soc., 1930, **52**, 1747).

Approximate relations between total pressure of an azeotropic mixture and temperature, and between the pressure and composition. From the second equation of (12), inserting $p_2 = N_2P$ (since the gases are perfect) and eliminating N_2 by means of equation (14), we have

$$\ln P = \ln p_2^\circ + \frac{Wab}{RT}\left[\tfrac{1}{2} + \frac{RT}{2Wab}\ln\frac{p_1^\circ}{p_2^\circ}\right]^2$$

As shown above $|p_1^\circ - p_2^\circ|$ is in general small; hence the term containing $(\ln p_1^\circ/p_2^\circ)^2$ on the right-hand side of the above equation can be neglected. Hence

$$\ln P \sim \ln p_2^\circ + \frac{Wab}{4RT}\left[1 + \frac{2RT}{Wab}\ln\frac{p_1^\circ}{p_2^\circ}\right]$$

$$\sim \frac{Wab - 2(H_1^\circ + H_2^\circ)}{4RT} + D$$

$$\sim A/RT + D \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

which is of the simple Clausius–Clapeyron form and shows that $-(1 - N_2)\bar{H}_1 + N_2\bar{H}_2$ in equation (3) is approximately constant for a strictly regular solution.

Elimination of T between (17) and (16) gives an equation relating azeotropic composition and pressure of the form

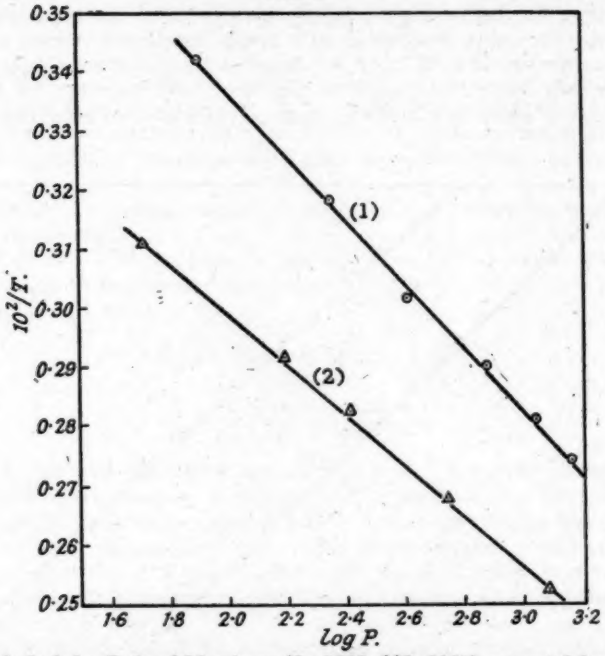
$$N_2 \sim A_1/(\ln P - D) + C_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

From (17), $D \longrightarrow \ln P$ as $T \longrightarrow \infty$ and hence $D > \ln P$ and we may write

$$N_2 \sim -\frac{A_1}{D\left(1 - \frac{\ln P}{D}\right) + C} \sim -\frac{A_1}{D}\left(1 + \frac{\ln P}{D}\right) + C \sim A'' \ln P + C'' \quad . \quad . \quad (19)$$

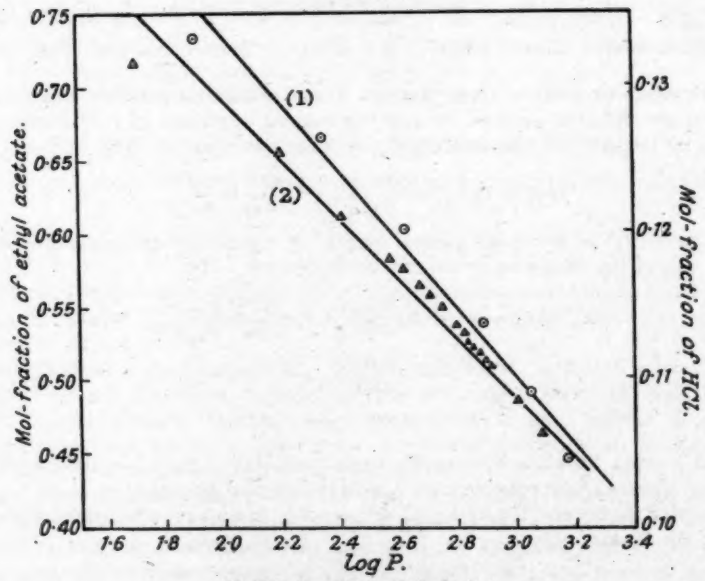
where A'' and C'' are constants.

FIG. 2.



(1) *Ethyl acetate–ethyl alcohol: Data of Merriman* (J., 1913, **103**, 1801) *as quoted by Carlson and Colburn* (Ind. Eng. Chem., 1942, **34**, 581).
(2) *Hydrogen chloride–water: Data of Bonner and Wallace* (J. Amer. Chem. Soc., 1930, **52**, 1747).

FIG. 3.



(1) *Ethyl acetate–ethyl alcohol.*
(2) *Hydrogen chloride–water.*

In Fig. 2, ln P is plotted against $1/T$ for the azeotropic systems ethyl acetate–ethyl alcohol and hydrogen chloride–water (the experimental values for P and T being taken from the data of Merriman, and of Bonner and Wallace, *locc. cit.*). A good straight line results in each case. In Fig. 3, N_2 is plotted against ln P for the same systems. Here the curves show definite

departures from linearity and it appears that equation (18) is not accurately approximated by equation (19). An alternative and more exact expression for the relationship between N_2 and $\ln P$ is discussed later [see equation (22)].

An Examination of Other Methods for the Calculation of Azeotropic Relationships.—Kireev (*loc. cit.*) has discussed the calculation of variations in azeotropic composition with temperature and pressure on the basis of equation (11). He suggests that for many solutions experimental values of ΔG^E satisfy an empirical relationship of the form $\Delta G^E = N_1N_2K^1$ where K^1 is a constant and independent of N_2 but possibly a function of T. It can readily be shown that this is equivalent to assuming that the properties of such solutions are described by the Margules–Porter equation at constant temperature. Thus, insertion of equations (12) in (9), which is true without restriction for any liquid solution, gives

$$\begin{aligned}\Delta G^E &= RT[N_1 \ln e^{Wab N_2^2/RT} + N_2 \ln e^{Wab N_1^2/RT}] \\ &= N_1N_2\,Wab \\ &= N_1N_2K^1 \text{ where } K^1 = Wab \quad \ldots\ldots\ldots\ldots \quad (20)\end{aligned}$$

Differentiation of (20) with respect to N_2 at constant T and combination with equation (11) yields

$$(1 - 2N_2)K^1 = RT \ln p_1^\circ/p_2^\circ \quad \ldots\ldots\ldots\ldots \quad (21)$$

which is necessarily identical with equation (14) already derived. Insertion of the azeotropic limitation in equation (9) by writing $p_1 = N_1P$ and $p_2 = N_2P$, combination with (20), and elimination of K^1 between the resulting equation and (21) gives

$$(1 - 2N_2)(\ln P - \ln p_1^\circ) = N_2^2 (\ln p_1^\circ - \ln p_2^\circ)$$

which can be solved for N_2 by adding $N_2^2(\ln P - \ln p_1^\circ)$ to both sides whence

$$(1 - N_2)^2 (\ln P - \ln p_1^\circ) = N_2^2(\ln P - \ln p_2^\circ)$$

$$\frac{(1 - N_2)^2}{N_2^2} = \frac{\ln P/p_2^\circ}{\ln P/p_1^\circ} = y$$

$$N_2^2 (1 - y) - 2N_2 + 1 = 0$$

and

$$N_2(\text{az.}) = \frac{1}{1 + \sqrt{y}} = \frac{1}{1 + \sqrt{\dfrac{\ln p_2^\circ - \ln P}{\ln p_1^\circ - \ln P}}} \quad \ldots\ldots\ldots\ldots \quad (22)$$

(The negative root of $\pm y$ is chosen in order to make $N_2 < 1$.)

Equation (22), which was first derived by Kireev, relates the composition of the azeotrope to its pressure and the vapour pressures of the pure components at the boiling point of the azeotrope. In the derivation no assumption regarding the temperature-dependence of K^1 (in equation 20) need be made, although, as we have seen, for strictly regular solutions K^1 should vary only slightly with temperature as it equals *Wab*. Kireev found that the equation satisfactorily correlated experimental data for a number of systems, which, as this discussion reveals, should be the case provided they satisfy the Margules–Porter equation at constant temperature.

The variation of composition with temperature was considered by Kireev on the basis of a suggestion that K^1T = constant = C_4 for certain solutions. Insertion of this condition in (21) and replacement of the $\ln p_1^\circ/p_2^\circ$ term by equivalent latent heat terms from the Clausius–Clapeyron equation yields

$$N_2\,(\text{az.}) = \tfrac{1}{2}\left[1 + \frac{H1 - H2}{C_4}\,T + C_5T^2\right] \quad \ldots\ldots\ldots\ldots \quad (23)$$

where $C_5 = (C_2 - C_1)R/C_4$ and C_1, C_2, and C_4 have been defined already.

This expression contains a term involving the square of the temperature, but if C_5 is small, or if the temperature ranges over which measurements are made is restricted, it may be difficult to detect a deviation from linearity due to the T^2 term in a plot of N_2 against T. In fact, experimental data for numerous systems are fitted by a linear relation, as has been shown already, and (23) will not be discussed further.

A method used by Carlson and Colburn (*Ind. Eng. Chem.*, 1942, **34**, 581) for calculating the change in the composition with temperature of the azeotrope ethyl acetate–ethyl alcohol involved several successive operations. First, the activity coefficients, γ_1 and γ_2, of the two components were evaluated from $\gamma_1 = P_{az.}/p_1^\circ$ and $\gamma_2 = P_{az.}/p_2^\circ$. Here, $P_{az.}$ is the total pressure at the

boiling point of the azeotrope and p_1° and p_2° are the vapour pressures of the pure components at this temperature. Data at atmospheric pressure were used for this calculation of γ_1 and γ_2, and the values so obtained were used to calculate the van Laar constants. From these constants the ratio γ_1/γ_2 was calculated at, and plotted against, different compositions at constant temperature and then, on the assumption that the van Laar constants are not dependent on temperature, the composition at other temperatures was found from the relationship $\gamma_1/\gamma_2 = p_2^\circ/p_1^\circ$, which is true for the azeotrope, in conjunction with the plot of γ_1/γ_2 against N_2. To facilitate the calculation, experimental values of p_1°/p_2° were plotted against temperature.

It is of interest to compare the calculations made in this way with those made more directly from equation (14). By rearrangement the latter equation yields

$$(2N_2 - 1) = \frac{(2N_2^* - 1)}{T^* (\ln p_1^\circ/p_2^\circ)^*} \times T \ln p_1^\circ/p_2^\circ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (24)$$

where the starred values refer to a known composition of the azeotrope (N_2^*) at one temperature (T^*). If for the pure components p_1°/p_2° is known as a function of T, then N_2, the azeotropic composition at any boiling point T, can be secured from equation (24).

In the table the observed values of N_2 and T (Merriman, *loc. cit.*) are compared with the calculated. The composition at 760 mm. pressure and at a temperature of 71·8° was taken as the known value in both calculations.

Ethyl acetate–ethyl alcohol azeotrope.

Composition, N_2 = mol.-fraction of ethyl acetate.

		Calculated.	
Temp.	Exptl.	by Carlson and Colburn.	by eqn. (24).
18·7°	0·734	0·787	0·706
40·5	0·660	0·677	0·639
56·3	0·601	0·602	0·596
71·8	0·539	(0·539)	(0·539)
83·1	0·490	0·498	0·500
91·4	0·451	0·480	0·480
Standard deviation of an individual calculated value :		0·022	0·019

Clearly, the experimental data are fitted as well by equation (24) as by the Carlson and Colburn procedure.

Validity of the Approximate Treatment.—It has been shown that all the methods of calculation we have discussed rest upon an assumption that either the Margules–Porter or the van Laar equation adequately describes the behaviour of the liquid–vapour systems at constant temperature. The methods of relating variation of azeotropic composition with temperature used by Kireev and by Carlson and Colburn have each an empirical element; Kireev takes K^1T as constant, and Carlson and Colburn assume that the A and B constants of the van Laar equations are temperature-independent—an assumption with no real theoretical justification.

Statistical thermodynamical reasoning suggests that the equations (12) which serve as basis for the present approximate treatment should describe to a good approximation the behaviour of strictly regular solutions.*

It follows from the definition of strictly regular solutions (p. 600), and from the conclusion that in general the boiling points of the components must be close together if an azeotrope is to exist, that an azeotrope formed between normal liquids will usually conform to the behaviour of a regular azeotrope and be described by the equations we have used. It is rather surprising,

* Since this manuscript was prepared, a memoir by Prigogine (*J. Phys. Radium*, 1944, **5**, 185) has become available. This author also considers azeotropes formed from strictly regular solutions and derives an equation equivalent to (14). He demonstrates that this equation is compatible with the empirical rule of Roozeboom connecting the direction of change of composition with temperature. The relationship between log P and $1/T$ is also studied. An equation of the type

$$\frac{N_2^2}{(1 - N_2)^2} = \left(\frac{H_1/T_1}{H_2/T_2}\right)\left(\frac{T_1 - T}{T_2 - T}\right)$$

is deduced where T_1 and T_2 are the boiling points of the pure components and T the boiling point of the azeotrope. The validity of the equation in the simple form where $H_1/T_1 = H_2/T_2$ was tested by using experimental data for azeotropes formed between halides and ethyl alcohol.

nevertheless, that some at least of the azeotropic mixtures containing associated components also appear to conform fairly closely to equations (16), (17), and (19) (*e.g.*, ethyl acetate–ethyl alcohol) and so also do some azeotropes in which one component is heavily solvated by the other (*e.g.*, hydrogen chloride–water).

A preliminary report on the relationships which we have derived has appeared in *Nature* (1946, **158**, 198).

The work described above has been carried out as part of the research programme of the Chemical Research Laboratory and this paper is published by permission of the Director of the Laboratory.

CHEMICAL RESEARCH LABORATORY,
TEDDINGTON, MIDDLESEX.

[*Received, July 25th*, 1946.]

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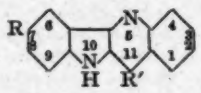
111. *Carbazoles, Carbolines, and Related Compounds. Part I. Quindoline Derivatives.*

By S. J. HOLT and V. PETROW.

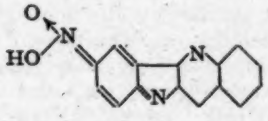
Improved methods for the preparation of quindoline [quinolo(2′ : 3′ : 3 : 2)indole] and its 11-carboxylic acid (I; R = H, R′ = CO_2H) have been developed. Bromination of these compounds has been found to give the *7-bromo*-derivatives, identical with the compounds obtained by direct synthesis from *5-bromo*-ON-*diacetylindoxyl* and isatin. Nitration of quindoline gives *7-nitro-* (I; R = NO_2; R′ = H), *11-nitro-* (I; R = H; R′ = NO_2), and *7 : x-dinitro-quindoline*. The constitution of the first followed from its reduction to *7-amino-quindoline* and conversion of the latter into 7-bromoquindoline. The structure of the second isomeride was determined by reduction to the amino-compound identical with *11-amino-quindoline* obtained from quindoline-11-carboxylic acid.

THE study of the chemistry of the heterocyclic ring systems of potential biological interest, now in progress in these laboratories, has been extended to the carbazole and azacarbazole (carboline) groups of compounds. Only 2-azacarbazole (β-carboline) has hitherto received any degree of attention, by virtue of its connection with the harmala alkaloids. We now report a study of some derivatives of quindoline (3 : 4-benz-8-carboline). Their conversion into quaternary salts, and a brief reference to their biological properties, will be reported in Part II (forthcoming publication).

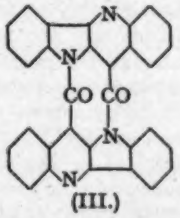
We were unable to obtain supplies of technical " indoxyl melt " required for the convenient preparation of quindoline-11-carboxylic acid described by Armit and Robinson (*J.*, 1922, **121**, 836), and so turned our attention to the alternative use of *ON*-diacetylindoxyl (" Friedländer," **5**, 940) and *N*-acetylindoxyl (*ibid*, p. 941). These two compounds have the added advantage of being very much less readily oxidised than the parent indoxyl. Condensation with isatinic acid in strongly alkaline solution led to formation of quindoline-11-carboxylic acid (I; R = H, R′ = CO_2H) in yields exceeding 90%. When lower concentrations of alkali were employed,



(I.)



(II.)



(III.)

variable amounts of indirubin were formed as a by-product. Both Fichter and Rohner (*Ber.*, 1910, **43**, 3489) and Armit and Robinson (*loc. cit.*) prepared quindoline (I; R = R′ = H) * from the 11-carboxylic acid by such methods as reduction with zinc dust in alkali, or with sodium amalgam, followed by oxidation with air. We now find that this procedure may be avoided, and the yield of quindoline raised above 90%, by direct decarboxylation of (I; R = H, R′ = CO_2H) at its melting point, or in liquid paraffin at 300°.

The bromination of quindoline has been studied by Fichter and Rohner (*loc. cit.*), who obtained a product to which they assigned the 7-bromo-structure (I; R = Br, R′ = H). As 10-acetylquindoline would not brominate under the same conditions, but gave an unstable

* The numbering of the quindoline ring system follows " The Ring Index " (Patterson and Capell).

" perbromide " which passed into the hydrobromide of 10-acetylquindoline on standing in air, they assumed the initial formation of 10-bromoquindoline, followed by rearrangement to the 7-bromo-isomeride. We have now confirmed structure (I; R = Br, R′ = H) by direct synthesis from 4-bromophenylglycine-*o*-carboxylic acid. It may be added that the formation of the latter compound by direct bromination of phenylglycine-*o*-carboxylic acid is claimed by the Badische Anilin- and Soda-Fabrik (G.P. 148,615), but evidence supporting this structure is not presented. We have now confirmed the constitution assigned to this compound by direct comparison with authentic 4-bromophenylglycine-*o*-carboxylic acid prepared by the method of Friedländer, Bruckner, and Deutsch (*Annalen*, 1912, **388**, 34). It gave *5-bromo*-ON-*diacetylindoxyl* together with some *5-bromo*-N-*acetylindoxyl* on ring closure, the diacetyl compound condensing with isatinic acid in alkaline solution to give *7-bromoquindoline-11-carboxylic acid* (I; R = Br, R′ = CO_2H), also identical with the product we obtained by direct bromination of quindoline-11-carboxylic acid, to which must therefore be assigned the 7-bromo-structure. Decarboxylation of these bromo-acids gave the same 7-bromoquindoline, identical with the bromoquindoline prepared by the method of Fichter and Rohner (*loc. cit.*), and yielding identical *acetyl* derivatives.

Reaction of quindoline-11-carboxylic acid with thionyl chloride gave *quindoline-11-carboxyl chloride hydrochloride*, converted by heating in nitrobenzene into a bimolecular *product*, $C_{32}H_{16}O_2N_4$. We have termed this compound *bisquindolinoyl*, and have assigned it structure (III), a formulation which agrees well with its mode of formation, its molecular weight (Rast method), and its reconversion into quindoline-11-carboxylic acid on alkaline hydrolysis. *Quindoline-11-carboxyamide* (I; R = H, R′ = $CO{\cdot}NH_2$) failed to yield the corresponding amine on hypobromite oxidation, owing probably to the small solubility of the base. In common with the simpler γ-carboxyamidoquinolines (cf. Petrow, *J.*, 1945, 19) it gave *11-cyanoquindoline* (I; R = H, R′ = CN) on sublimation.

11-Aminoquindoline (I; R = H, R′ = NH_2), prepared from the acid by the Curtius method, resembled 5-aminoacridine in that its dilute solutions were highly fluorescent, and reacted alkaline to litmus. Thus the pH of a 0·003M-solution in 50% alcohol was found to be 9·6. It formed only a *monohydrochloride*, and on acetylation gave a *triacetyl* derivative which was highly fluorescent in ultra-violet light (cf. Wilkinson and Finar, *J.*, 1946, 116).

The nitration of quindoline was studied by Fichter and Rohner (*loc. cit.*; see also Giraud, *Compt. rend.*, 1880, **90**, 1430), who described the formation of an orange dinitroquindoline. On repeating this work it soon became apparent that this was actually a mixture of two mononitroquindoline nitrates. These were separated by chromatographic adsorption on alumina, with benzene as solvent and elution agent, into a more strongly adsorbed yellow mononitroquindoline (80%) and a scarlet isomeride (10%). As indole derivatives usually nitrate *para*- to the indole nitrogen, we assigned the constitution of a *7-nitroquindoline* (I; R = NO_2, R′ = H) to the yellow mononitration product. This assumption was supported by the behaviour of the compound with sodium hydroxide solution, whereupon, in common with such related compounds as 3-nitrocarbazole (cf. Stevens and Tucker, *J.*, 1923, 2141), a deep red coloration was obtained. This result is no doubt due to the formation of a salt of the ψ-nitro-acid (II). Attempts to confirm this structure by direct synthesis from 5-nitrodiacetylindoxyl were not successful. Although the necessary 4-nitrophenylglycine-*o*-carboxylic acid required for the preparation of the latter compound has been described by Hartmann (Diss., Halle, 1914, p. 41), in our hands the method gave poor yields (29%), and the same compound was finally obtained in 65% yield by direct condensation of 2-chloro-5-nitrobenzoic acid (Rupe, *Ber.*, 1897, **30**, 1099) with glycine by means of a copper-bronze catalyst. Ring closure gave *5-nitro*-ON-*diacetylindoxyl*, but this compound failed to undergo the required condensation with isatinic acid. It was thought that removal of the *O*-acetyl group might facilitate the condensation, but attempts to carry this out using the " sulphite hydrolysis method " (Bayer & Co., G.P. 108,761) were unsuccessful. An alternative route would involve reduction of *o*-nitrobenylidene-5-nitroindoxyl, but attempts to prepare this compound from 5-nitrodiacetylindoxyl and *o*-nitrobenzaldehyde gave inconclusive results. The structure of the yellow mononitroquindoline was finally established by reduction to the amino-compound, followed by conversion into the bromoquindoline, which was found to be identical with the 7-bromo-isomeride (above). *7-Aminoquindoline* (I; R = NH_2, R′ = H) was characterised by conversion into a *triacetyl* derivative and by formation of *7-benzylideneaminoquindoline* (I; R = N:CHPh, R′ = H).

In contrast to 7-nitroquindoline, which readily gave an *acetyl* derivative, the scarlet nitroquindoline (above) resisted all attempts at acetylation, including the drastic conditions successfully employed by Preston, Tucker, and Cameron (*J.*, 1942, 500) for 1-nitrocarbazole.

It gave a weak purple coloration with alkali. Its formulation as an 11-*nitroquindoline* (I; R = H, R′ = NO_2) followed from its reduction to 11-aminoquindoline. The nitration of quindoline in the 11-position finds a parallel in the reported formation of 4-nitro-3-acetamidoquinoline from 3-acetamidoquinoline (Renshaw and Friedman, *J. Amer. Chem. Soc.*, 1939, **61**, 3320), although the quinoline derivative differs in its resistance to reduction. It is noteworthy that nitration of quindoline may be effected with dilute nitric acid. For instance, prolonged heating with 0·5N-nitric acid gave the scarlet isomeride exclusively in 10% yield, with recovery of unchanged quindoline. The use of 2N-nitric acid gave the mixed isomers. A method is described for the exclusive preparation of each isomer in satisfactory yield. Nitration of quindoline-11-carboxylic acid gave the *nitrate* of 7-nitroquindoline-11-carboxylic acid (I; R = NO_2, R′ = CO_2H) The free *acid* gave 7-nitroquindoline on decarboxylation, and 7-*aminoquindoline*-11-*carboxylic acid* (I; R = NH_2, R′ = CO_2H) on reduction. Nitration of quindoline with boiling concentrated nitric acid gave a low yield of 7 : x-*dinitroquindoline*, also formed by further nitration of 7-nitroquindoline, but not obtained from the 11-nitro-isomeride.

Experimental.

(M. p.'s are corrected; semimicroanalyses are by Mr. S. Bance, B.Sc., A.R.I.C., Microanalytical Dept., May and Baker Ltd.).

Quindoline-11-*carboxylic Acid* (I; R = H, R′ = CO_2H).—A cooled solution of isatin (85 g.) in potassium hydroxide (515 g.) and water (2300 ml.) was run into a flask containing *N*-acetylindoxyl (100 g.) (or *ON*-diacetylindoxyl, 124 g.) in an atmosphere of coal-gas, and the mixture shaken until solution was complete. After 10 days water (1000 ml.) was added to the greenish-yellow crystalline mass, and air passed through the heated solution for 20 minutes, whereby any excess of indoxyl was oxidised to indigo. Concentrated hydrochloric acid was added to the hot filtrate with thorough stirring until a faint permanent precipitate was formed, followed by addition of charcoal (10 g.). The filtrate was added to an equal volume of alcohol, and the solution made acid to litmus with concentrated hydrochloric acid, giving quindoline-11-carboxylic acid, which was collected and washed twice with hot water and with alcohol. For further purification the crude acid in hot 2N-sodium hydroxide (300 ml.) and water (200 ml.) was treated with dilute hydrochloric acid until a slight permanent precipitate was obtained, charcoal (10 g.) added, and after addition of an equal volume of alcohol to the filtrate, concentrated hydrochloric acid added until the mixture was acid to litmus. Quindoline-11-carboxylic acid formed a bright yellow powder, m. p. 336—337° (decomp.) (Found : C, 73·4; H, 3·8; N, 10·9. Calc. for $C_{16}H_{10}O_2N_2$: C, 73·3; H, 3·8; N, 10·7%); yield 140 g. Its hydrochloride was obtained as a *monohydrate* (Found : N, 9·0; Cl, 11·2. $C_{16}H_{11}O_2N_2Cl,H_2O$ requires N, 8·9; Cl, 11·2%), an orange powder, when quindoline-11-carboxylic acid (2 g.) was heated under reflux for 1 hour with 5N-hydrochloric acid (5000 ml.), and the rapidly filtered solution allowed to cool. On heating, it lost hydrogen chloride to give the free acid. When quindoline-11-carboxylic acid (40 g.) in liquid paraffin (300 ml.) was kept at 290—300° until evolution of carbon dioxide had ceased with almost complete solution, and an equal volume of light petroleum (b. p. 40—60°) added to the cooled mixture, quindoline was obtained as yellow plates from toluene (1250 ml.), m. p. 251—252° (Found : C, 82·6; H, 4·3; N, 12·9. Calc. for $C_{15}H_{10}N_2$: C, 82·6; H, 4·6; N, 12·9%); yield 31·2 g.

5-*Bromo*-ON-*diacetylindoxyl*.—4-Bromophenylglycine-*o*-carboxylic acid (20 g.) was added in small portions to boiling acetic anhydride (100 ml.) containing fused sodium acetate (9·5 g.). After a further 5 mins. an equal volume of water was added, and the decomposed mixture decanted from a small quantity of tarry material. On cooling, crude 5-*bromo*-ON-*diacetylindoxyl* (12 g.) was obtained, separating from acetic anhydride in white needles, m. p. 124—124·5° (Found : C, 48·7; H, 3·4; N, 4·8; Br, 27·2. $C_{12}H_{10}O_3NBr$ requires C, 48·7; H, 3·4; N, 4·7; Br, 27·0%); yield 7·2 g. (33%). Decomposition of the acetic anhydride mother-liquors with water gave 5-*bromo*-N-*acetylindoxyl*, needles from methanol, m. p. 187—188° (Found : C, 47·3; H, 3·3; N, 5·7; Br, 31·7. $C_{10}H_8O_2NBr$ requires C, 47·2; H, 3·2; N, 5·5; Br, 31·5%); yield 900 mg.

7-*Bromoquindoline*-11-*carboxylic Acid* (I; R = Br, R′ = CO_2H).—(*a*) 5-Bromo-*ON*-diacetylindoxyl was condensed with potassium isatinate (as above), and 7-*bromoquindoline*-11-*carboxylic acid* was obtained as an orange amorphous powder, m. p. 328—329° (decomp.) (Found : C, 56·3; H, 2·9; N, 8·1; Br, 23·2. $C_{16}H_9O_2N_2Br$ requires C, 56·4; H, 2·6; N, 8·2; Br, 23·4%); yield 88%. (*b*) Quindoline-11-carboxylic acid (3·5 g.) was triturated with glacial acetic acid (25 ml.), and a solution of bromine (1·6 ml.) in glacial acetic acid (10 ml.) added with stirring. The yellow suspension thickened and became purple. After 1 hour, water (100 ml.) was added, the precipitated solids were collected, washed with water, and dissolved in 2N-sodium hydroxide, and the solution boiled for 5 mins. and filtered. An equal volume of alcohol was added, followed by concentrated hydrochloric acid–alcohol (1 : 1) until a faint permanent precipitate was obtained. Charcoal was added, and 7-bromoquindoline-11-carboxylic acid obtained by addition of hydrochloric acid to the filtrate until acid to litmus (Found : N, 8·1; Br, 23·6%), m. p. 328—329° (decomp.), alone or in admixture with the bromo-acid prepared by method (*a*); yield 4 g. (87%).

7-*Bromoquindoline* (I; R = Br, R′ = H).—(*a*) Decarboxylation of 7-bromoquindoline-11-carboxylic acid in liquid paraffin at 285° gave 7-bromoquindoline in yellow needles or plates from alcohol, m. p. 314·5—315° (Found : C, 60·5; H, 3·0; N, 9·6; Br, 26·5. Calc. for $C_{15}H_9N_2Br$: C, 60·6; H, 3·0; N, 9·4; Br, 26·9%); yield 81%. (*b*) A solution of bromine (5 g.) in glacial acetic acid (100 ml.) was slowly added with stirring to quindoline (3·3 g.) in glacial acetic acid (66 ml.). The orange-yellow perbromide was collected, washed with water and, on warming with N-ammonium hydroxide, gave 7-bromoquindoline, identical in m. p. and mixed m. p. with the compound prepared by method (*a*). Fichter and Rohner (*loc. it.*) give m. p. 304°.

The *acetyl* derivative, pale yellow needles from alcohol, m. p. 174—174·5° (Found: N, 8·2. $C_{17}H_{11}ON_2Br$ requires N, 8·3%), was prepared by heating 7-bromoquindoline (1·5 g.) with acetic anhydride (15 ml.) for 35 minutes.

Derivatives of Quindoline-11-carboxylic Acid.—*Quindoline-11-carboxyl chloride hydrochloride* obtained (95% yield) when the pure acid was heated under reflux with thionyl chloride for 2 hours, formed a micro-crystalline scarlet powder which slowly lost hydrogen chloride on exposure to air (Found: Cl, 22·1. $C_{16}H_{10}ON_2Cl_2$ requires Cl, 22·4%).

Bisquindolinoyl (III), squat pale yellow needles from xylene, m. p. 365—367° [Found: C, 78·6; H, 3·2; N, 11·8; *M* (Rast), 466. $C_{32}H_{16}O_2N_4$ requires C, 78·7; H, 3·3; N, 11·5%; *M*, 488·5], was obtained when quindoline-11-carboxyl chloride hydrochloride (12 g.) was heated under reflux in nitrobenzene (25 ml.) until evolution of hydrogen chloride had ceased (*ca.* 45 mins.). On hydrolysis with 2N-sodium hydroxide for 10 hours, quindoline-11-carboxylic acid was obtained, m. p. 336—337°, alone or in admixture with an authentic specimen. Decarboxylation gave quindoline.

Methyl quindoline-11-carboxylate, yellow matted needles from 50% methanol, m. p. 154—155° (Found: N, 9·8. OMe, 10·8; Loss on drying, 3·2. $C_{17}H_{12}O_2N_2,\frac{1}{2}H_2O$ requires N, 9·8; OMe, 10·9; H_2O, 3·2%. The dried sample gave N, 10·4; OMe, 11·2. $C_{17}H_{12}O_2N_2$ requires N, 10·2; OMe, 11·2%), was obtained when the 11-carboxyl chloride hydrochloride (5 g.) in dry methanol (50 ml.) was heated under reflux for 30 mins.

Quindoline-11-carboxyamide, a very sparingly soluble yellow powder, m. p. 334—336° (Found: C, 73·6; H, 4·1; N, 16·0. $C_{16}H_{11}ON_3$ requires C, 73·5; H, 4·2; N, 16·1%), was prepared by sublimation at 300°/0·1 mm. of the product obtained when ammonium hydroxide (20 ml., *d* 0·880) was added to the acid chloride hydrochloride (5 g.); yield 3 g. (78%). Sublimation of the amide at 300° gave *11-cyanoquindoline*, sparingly soluble yellow needles, m. p. 296° (Found: C, 79·0; H, 3·9; N, 17·6. $C_{16}H_9N_3$ requires C, 79·1; H, 3·7; N, 17·3%); yield 3·75 g. (81%). 11-Cyanoquindoline was also obtained (80%) when the amide (3 g.) was heated under reflux with acetic anhydride (20 ml.) for 1½ hrs., or (54%) when the amide (1 g.) was heated under reflux with phosphorus pentoxide (2 g.) in xylene (20 ml.).

11-Aminoquindoline (I; R = H, R′ = NH_2).—The following experimental conditions must be strictly adhered to: Pure quindoline-11-carboxyl chloride hydrochloride (7·9 g.) was added to 95% hydrazine hydrate solution (7·5 ml.) in water (75 ml.) and stirred at 40—50° until a homogeneous suspension of the hydrazide was obtained. The filtered and water-washed product was stirred with N-hydrochloric acid (400 ml.) at 0° until a *homogeneous* suspension of the hydrazide hydrochloride was obtained. Sodium nitrite (2·0 g.) in a little water was then slowly added, and after 30 mins.' stirring at 0° the red azide was rapidly collected on a previously cooled 18-cm. Buchner filter. The cake of azide was washed with ice-water, and heated with 2N-hydrochloric acid (400 ml.) in a large beaker. Rapid evolution of nitrogen occurred with considerable frothing. After cooling, the crude amine hydrochloride was collected, recrystallised once (charcoal) from 50% alcohol (400 ml.), and the purified salt (6·35 g.) decomposed by warming with 2N-ammonium hydroxide. *11-Aminoquindoline* formed yellow needles from 50% alcohol, m. p. *ca.* 297° (with previous blackening) (Found: C, 74·8; H, 4·7; N, 17·5; loss on drying, 3·7. $C_{16}H_{11}N_3,\frac{1}{2}H_2O$ requires C, 74·5; H, 4·9; N, 17·4; H_2O, 3·7%. The dried material gave N, 17·9. $C_{16}H_{11}N_3$ requires N, 18·0%); yield, 4·4 g. (83%). The *hydrochloride*, yellow needles from 50% alcohol, m. p. 350—380° (decomp.) (Found: N, 14·6; Cl, 12·2; loss on drying, 6·4. $C_{15}H_{12}N_3Cl,H_2O$ requires N, 14·6; Cl, 12·3; H_2O, 6·3%), was obtained when 11-aminoquindoline (400 mg.) in boiling alcohol (40 ml.) was treated with hot 2N-hydrochloric acid (4 ml.) in water (36 ml.). The *triacetyl* derivative formed colourless plates from alcohol, m. p. 190—191° (Found: C, 70·2; H, 4·9; N, 11·8. $C_{21}H_{17}O_3N_3$ requires C, 70·2; H, 4·7; N, 11·7%).

7-Nitroquindoline (I; R = NO_2, R′ = H).—Quindoline (5 g.) was triturated with nitric acid (85 ml., *d* 1·42) at 0°, and after 12 hours at 15°, water (100 ml.) was added and the solids collected and basified by warming with N-ammonium hydroxide. The crude 7-nitro-derivative (5·8 g.) was freed from some 11-nitro-isomeride by heating it under reflux with chlorobenzene (100 ml.) for 30 mins. and allowing it to cool to 40°; it was then quickly collected and recrystallised from pyridine (40 ml.). Pyridine of crystallisation was removed in a vacuum over concentrated sulphuric acid, giving *7-nitroquindoline*, flattened yellow needles on sublimation at 320°/11 mm., m. p. 322—323° (Found: C, 68·3; H, 3·5; N, 15·9. $C_{15}H_9O_2N_3$ requires C, 68·4; H, 3·4; N, 16·0%); yield, 66%. The acetic acid addition *compound* formed long yellow needles (Found: C, 63·1; H, 4·5; N, 12·8; loss on drying, 18·6. $C_{15}H_9O_2N_3,CH_3{\cdot}CO_2H$ requires C, 63·2; H, 4·0; N, 13·0; HOAc, 18·4%), losing acetic acid on warming. The *acetyl* derivative formed very pale yellow needles from glacial acetic acid, m. p. 259—260° (Found: N, 13·7. $C_{17}H_{11}O_3N_3$ requires N, 13·8%).

7-Aminoquindoline (I; R = NH_2, R′ = H).—7-Nitroquindoline (7 g.), reduced iron (21·5 g.), anhydrous calcium chloride (1·35 g.), and 70% alcohol (105 ml.) were heated under reflux for 12 hrs. The mixture was immediately filtered into ice-cold, air-free water (110 ml.). Yellow needles were deposited on shaking (5·65 g.) which on recrystallisation from the minimum quantity of 50% alcohol gave, by rapid cooling and stirring, *7-aminoquindoline*, orange-yellow glittering plates, m. p. 274·5° (preheated bath) (Found: C, 77·1; H, 5·0; N, 17·8. $C_{15}H_{11}N_3$ requires C, 77·2; H, 4·8; N, 18·0%); yield, 4·6 g. The compound undergoes rapid oxidation in hot solution. The *triacetyl* derivative formed very pale yellow needles from alcohol, m. p. 237—238° (Found: C, 70·1; H, 5·0; N, 11·7. $C_{21}H_{17}O_3N_3$ requires C, 70·2; H, 4·7; N, 11·7%). *7-Benzylideneaminoquindoline*, bright yellow spangles from alcohol, m. p. 270—271° (Found: C, 81·8; H, 4·7; N, 13·2. $C_{22}H_{15}N_3$ requires C, 82·1; H, 4·7; N, 13·1%), was obtained when 7-aminoquindoline (580 mg.) in 2N-hydrochloric acid (2·5 ml.) and water (40 ml.) was treated with benzaldehyde (300 mg.), followed by crystalline sodium acetate (5·0 g.), and the mixture shaken for 20 minutes.

For conversion into 7-bromoquindoline, finely powdered anhydrous 7-aminoquindoline (1·17 g.) was added to 30% (w./v.) hydrobromic acid solution (30 ml.), and the suspension stirred at 0° for 15 minutes. Sodium nitrite (345 mg.) was then slowly added at 0°, and stirring continued for a further 30 mins. at this temperature. The suspension was then added to a solution of cuprous bromide (900 mg.) and

sodium bromide (1·2 g.) in 30% (w./v.) hydrobromic acid solution at 0°. The mixture was warmed on the water-bath until evolution of nitrogen had ceased, an equal volume of water added, and the solids collected, basified by warming with N-ammonium hydroxide, and extracted with boiling alcohol (50 ml.), giving 7-bromoquindoline, m. p. 314·5—315° (Found: N, 9·4; Br, 26·6. Calc. for $C_{15}H_9N_2Br$: N, 9·4; Br, 26·9%), not depressed in admixture with an authentic specimen; yield, 22%. The acetyl derivative, m. p. 174—174·5°, gave no depression in admixture with an authentic specimen.

*5-Nitro-*ON-*diacetylindoxyl.*—4-Nitrophenylglycine-*o*-carboxylic acid, long yellow needles from water, m. p. 226—227° in a sealed tube (lit. 226—227°) (Found: loss on drying, 13·2. Calc. for $C_9H_8O_6N_2,2H_2O$: H_2O, 13·0%. Found for dried product: C, 45·0; H, 3·4; N, 11·6. Calc. for $C_9H_8O_6N_2$: C, 45·0; H, 3·4; N, 11·7%), was prepared by heating 2-chloro-5-nitrobenzoic acid (10 g.), glycine (5·0 g.), anhydrous sodium carbonate (5·5 g.), copper powder (1·0 g.), and water (100 ml.) under reflux for 2 hours. The hot filtered solution was cooled, and the acid precipitated by addition of concentrated hydrochloric acid until the solution was acid to Congo-red. When the anhydrous acid was added to boiling acetic anhydride–sodium acetate as described above, it gave *5-nitro-*ON-*diacetylindoxyl*, light yellow plates from glacial acetic acid, m. p. 219—220° (Found: C, 54·8; H, 4·0; N, 10·5. $C_{13}H_{10}O_6N_2$ requires C, 55·0; H, 3·8; N, 10·7%); yield 57%.

11-*Nitroquindoline* (I; R = H, R′ = NO_2).—Nitric acid (0·64 g., *d* 1·52) in glacial acetic acid (10 ml.) was added, during 60 mins., to a boiling, well-stirred solution of quindoline (2·18 g.) in glacial acetic acid (20 ml.). Heating under reflux was continued for 30 mins. after addition was complete. Water (100 ml.) was added to the cooled mixture, and the solids collected and extracted with boiling benzene (500 ml.). The cold filtered extract was passed through a column of alumina (2·5 × 15 cm.). The orange-red band was eluted with benzene, and the solution concentrated to 50 ml., giving 11-*nitroquindoline*, magnificent scarlet silky needles, m. p. 282° (Found: C, 68·3; H, 3·4; N, 16·1. $C_{15}H_9O_2N_3$ requires C, 68·4; H, 3·4; N, 16·0%); yield 400 mg. (15%). Reduction with reduced iron gave 11-aminoquindoline (Found: C, 74·4; H, 4·6; N, 17·5; loss on drying, 3·7. Calc. for $C_{15}H_{11}N_3,\frac{1}{4}H_2O$: C, 74·5; H, 4·9; N, 17·4; H_2O, 3·7%. Found for dried material: N, 18·0. Calc.: N, 18·0%), identical with authentic 11-aminoquindoline, and converted into an identical triacetyl derivative.

7 : x-*Dinitroquindoline.*—Quindoline (5 g.) in nitric acid (80 ml., *d* 1·42) was heated under reflux for 15 mins. Water (10 ml.) was added, and when cold, the solids (5·1 g.) were collected and warmed for a few minutes with ammonium hydroxide. The product was crystallised from pyridine (90 ml.)–light petroleum (90 ml., b. p. 60—80°), then dissolved in hot pyridine (20 ml., charcoal), and light petroleum (10 ml.; b. p. 80—100°) added. 7 : x-*Dinitroquindoline* formed orange micro-needles, m. p. 303° (Found: C, 58·7; H, 3·0; N, 18·4. $C_{15}H_8O_4N_4$ requires C, 58·5; H, 2·6; N, 18·2%); yield, 1·5 g. (21%). The same compound (Found: N, 18·3%) was obtained when 7-nitroquindoline (3 g.) and nitric acid (40 ml., *d* 1·42) were heated under reflux for 15 mins., and water (5 ml.) added.

7-*Nitroquindoline*-11-*carboxylic acid.*—Quindoline-11-carboxylic acid (10 g.) was heated with nitric acid (80 ml., *d* 1·42) on the water-bath until solution was complete. After cooling, the solids were collected, washed with concentrated nitric acid, and dried over potassium hydroxide in a vacuum. 7-*Nitroquindoline*-11-*carboxylic acid nitrate* formed orange-yellow microcrystals, m. p. 332° (with previous darkening) (Found: C, 51·9; H, 3·0; N, 15·3. $C_{16}H_{10}O_7N_4$ requires C, 51·9; H, 2·7; N, 15·1%); yield, 11 g. (71%). The free *acid* formed a yellow, sparingly soluble, amorphous powder, m. p. 334—335° (sinters 327°) (Found: N, 13·6. $C_{16}H_9O_4N_3$ requires N, 13·7%). Decarboxylation of the acid (1 g.) gave 7-nitroquindoline, m. p. 332—333° (Found: N, 16·0%), not depressed in admixture with an authentic specimen; yield, 500 mg. (58%). 7-*Aminoquindoline*-11-*carboxylic acid*, a sparingly soluble, purplish-brown, amorphous powder, m. p. 311—312° (Found: C, 64·9; H, 4·4; N, 14·3; loss on drying, 6·0. $C_{16}H_{11}O_2N_3,H_2O$ requires C, 65·0; H, 4·4; N, 14·3; H_2O, 6·1. Found for dried product: N, 15·1. $C_{16}H_{11}O_2N_3$ requires N, 15·2%), was prepared by reduction of the nitro-acid with reduced iron, the filtrate made alkaline, warmed for 30 mins., filtered (charcoal), the new filtrate acidified with hydrochloric acid to Congo-red, and the amino-acid precipitated by addition of sodium acetate (30 g.); yield, 2·3 g. (78%).

Fluorescence of Quindoline Derivatives in Ultra-violet Light.—In general quindoline derivatives fluoresce both in the solid state and in solution. The colours vary from orange to dark blue.

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112. *The Structure of Clavatol, a Metabolic Product of* Aspergillus clavatus.

By C. H. HASSALL and A. R. TODD.

Clavatol, isolated from cultures of *Aspergillus clavatus* by Bergel, Moss, Morrison, and Rinderknecht (*J.*, 1944, 417), has been identified by degradation and synthesis as 2 : 4-*dihydroxy*-3 : 5-*dimethylacetophenone.*

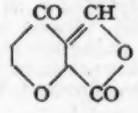
IN the course of experiments on the production of clavatin (patulin) (I) by the mould *Aspergillus clavatus*, when grown on synthetic media containing glucose, Bergel, Moss, Morrison, and Rinderknecht (*J.*, 1944, 417) observed the formation of small quantities of a phenolic substance,

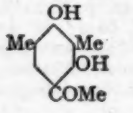
clavatol, which could be separated from clavatin by reason of its low solubility in water. As clavatol had no antibiotic properties and was produced in very small amount by the mould it was not exhaustively studied by these authors. It seemed, however, desirable that its structure should be investigated and its relationship, if any, to clavatin established, and we have therefore carried out the investigation here reported.

Clavatol, $C_{10}H_{12}O_3$, behaved on titration with alkali as a monohydric phenol, and in accordance with this behaviour it yielded a *monomethyl ether* and a *mono-acetate*. Since it resisted catalytic hydrogenation at atmospheric pressure it evidently contained no ethylenic linkage. From these facts it was evident that it must contain a second ring in addition to the phenolic nucleus, or, alternatively, one of the two oxygens, as yet unaccounted for, must be present in a carbonyl group resistant to hydrogenation. Clavatol failed to react with the usual carbonyl reagents, but the possibility that it might nevertheless be a ketone remained; it gave a strong purple ferric reaction and a positive iodoform reaction, although it gave no colouration with the nitro-chromic reagent (Fearon and Mitchell, *Analyst*, 1932, **57**, 372) for alcoholic hydroxyl groups. An added point in favour of the presence of a concealed keto-group (as in, *e.g.*, various resacetophenone derivatives) was the stability of clavatol to heating with concentrated mineral acid or alkali fusion; such stability would hardly be expected in a compound containing oxygen either in a heterocyclic nucleus or in a simple ether linkage.

Taking all the above facts into account it seemed to us that clavatol might well be a resacetophenone derivative in which only one of the phenolic hydroxyl groups was capable of ready detection. Accordingly a small amount of the substance was treated in alkaline solution with hydrogen peroxide. The solution thus obtained yielded on acidification and treatment with 2 : 4-dinitrophenylhydrazine *3-hydroxy-2 : 6-dimethylbenzoquinone 2 : 4-dinitrophenylhydrazone*, identical with a synthetic specimen. It was therefore concluded that clavatol itself is *2 : 4-dihydroxy-3 : 5-dimethylacetophenone* (II) (*3 : 5-dimethylresacetophenone*). Synthesis of (II) by applying the Hoesch reaction to 2 : 4-dimethylresorcinol gave a product identical in all respects with natural clavatol.

The production of clavatol together with clavatin by *A. clavatus* recalls the observation that clavatin is also accompanied by two simple phenolic compounds (gentisyl alcohol and gentisic acid) in cultures of *P. patulum* (Birkinshaw, Bracken, and Raistrick, *Biochem. J.*, 1943, **37**, 726). Clavatol seems to us of particular interest since it is the first simple resacetophenone derivative identified as a product of mould metabolism. Compounds of this type might well act as intermediates in the biosynthesis of anthoxanthin pigments; such pigments have not as yet been found in fungi, although one mould pigment, citromycetin, appears on present evidence to be a related benzo-γ-pyrone derivative (Raistrick, *Phil. Trans.*, 1931, *B*, **220**, 1).

(I.) 



(II.)

Experimental.

Clavatol.—Isolated as described by Bergel, Moss, Morrison, and Rinderknecht (*loc. cit.*), clavatol forms needles from aqueous methanol. It can be sublimed in a high vacuum and then forms lustrous colourless plates, m. p. 183° [Found : C, 66·3; H, 6·8; *M* (Rast), 188. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%; *M*, 180]. It dissolves in sodium hydroxide (equiv. by titration, 176—182), sodium carbonate, or ammonia with a yellow colour and gives a purple ferric reaction destroyed by acids. Clavatol gives no reaction with diazotised sulphanilic acid or with 2 : 6-dichloroquinone-chloroimide. On oxidation with potassium permanganate it yields acetic and oxalic acids.

Clavatol Monomethyl Ether.—Prepared by treating clavatol with diazomethane or with methyl sulphate and sodium hydroxide, the *ether* has m. p. 35—36° (b. p. 90°/0·6 mm.) (Found : C, 68·2, 68·6; H, 7·3, 7·2; OMe, 15·0, 16·6. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2; OMe, 16·0%).

Clavatol Acetate.—Prepared in the usual manner with acetic anhydride in pyridine solution, the *acetate* crystallises from aqueous methanol in colourless prisms, m. p. 95—96° (Found : C, 64·2; H, 6·2. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%).

Oxidation of Clavatol with Hydrogen Peroxide.—Clavatol (0·188 g.) was dissolved in a minimum amount of 0·1N-sodium hydroxide, and aqueous hydrogen peroxide (5 c.c. containing 0·034 g.) was added dropwise during 15 minutes. The intensely purple solution was set aside for two hours then acidified with dilute sulphuric acid. Unchanged clavatol (0·1 g.) was removed by filtration and the bright yellow filtrate extracted with ether. Evaporation of the ethereal extract gave orange needles (20 mg.) which on treatment with saturated aqueous 2 : 4-dinitrophenylhydrazine hydrochloride gave a red precipitate. Thrice recrystallised from alcohol, the *2 : 4-dinitrophenylhydrazone* formed deep red plates or needles, m. p. 243° (decomp.) (Found : C, 51·0; H, 3·7; N, 16·6. $C_{14}H_{12}O_6N_4$ requires C, 50·6; H, 3·6; N, 16·8%). When 3-hydroxy-2 : 6-dimethylbenzoquinone (Fittig and Sieperman, *Annalen*, 1875, **180**, 27) was treated with 2 : 4-dinitrophenylhydrazine hydrochloride in the same way, it yielded a

2 : 4-dinitrophenylhydrazone identical in m. p. (243°) and mixed m. p. with the above product from clavatol (Found : C, 50·9; H, 3·9; N, 16·7%).

2 : 4-*Dihydroxy*-3 : 5-*dimethylacetophenone* (*Clavatol*).—2 : 4-Dimethylresorcinol was prepared by catalytic hydrogenation of resorcinol-2 : 4-dialdehyde (Baker, Kirby, and Montgomery, *J.*, 1932, 2876) using a palladium oxide catalyst. This catalyst was much more effective (yield 94%) than the palladised charcoal recommended by Asahina and Nonomura (*J. Pharm. Soc. Japan*, 1934, **54**, 79), the use of which was accompanied by extensive polymerisation.

2 : 4-Dimethylresorcinol (1·8 g.) was dissolved in dry ether (10 c.c.) to which had been added methyl cyanide (1·0 g.) and powdered anhydrous zinc chloride (0·8 g.). The mixture was cooled in ice, and dry hydrogen chloride was passed through it for 3 hours, by which time a red solid had separated. The flask containing the reaction mixture was sealed and set aside overnight in a refrigerator. The red solid was then collected, washed with ether, and dissolved in water (50 c.c.), and the solution was boiled for 30 minutes. The solid (m. p. 175°) which had separated (1·48 g.; 68%) was collected, dried, and purified by sublimation in a high vacuum; it then formed lustrous plates, m. p. 183°, undepressed in admixture with natural clavatol (Found : C, 66·8; H, 6·5. $C_{10}H_{12}O_2$ requires C, 66·7; H, 6·7%). The acetate of the synthetic 2 : 4-*dihydroxy*-3 : 5-*dimethylacetophenone* had m. p. 95—96°, undepressed by clavatol acetate (m. p. 95—96°).

The clavatol used in this investigation was obtained through the courtesy of the Research Department, Roche Products Ltd.; we are also indebted to the members of that Department for making available such analytical and other data as were obtained by them in their earlier work on *A. clavatus*.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 1st*, 1946.]

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113. *Some Amines and Amides derived from Vanillin.*

By A. A. L. CHALLIS and G. R. CLEMO.

A number of derivatives of vanillylamine (3-methoxy-4-hydroxybenzylamine) have been prepared including the chaulmoogroyl and sulphanilamides. Other benzylamines and homobenzylamines have been converted into the N^1-benzylsulphanilamides. Vanillinanil has been aminated and the sulphanilamidine prepared. Vanillylidenecyanoacetic ester and its aniline condensation compound were converted by way of the imino-chloride into the corresponding amidine hydrochlorides. All these compounds have been or will be tested biologically; the results so far known are recorded.

[No formulæ are printed for compounds (I)—(XIV). They can be obtained by placing the groups indicated in positions 1, 2, 3, and 4 in the benzene ring (see Table I).]

VANILLYLAMINE (I) was prepared from vanillin oxime by Nelson's method (*J. Amer. Chem. Soc.*, 1919, **41**, 1118). Condensation of this amine with long-chain fatty acid chlorides gave *amides* of type (II) related to capsaicin (III), which when volatilised had a strong sternutatory action and also produced a hot taste at the back of the throat.

TABLE I.

Compound.	Position in benzene ring. 1.	2.	3.	4.
I	OH	OMe	H	$CH_2{\cdot}NH_2$
II	OH	OMe	H	$CH_2{\cdot}NH{\cdot}CO{\cdot}$Alk
III	OH	OMe	H	$CH_2{\cdot}NH{\cdot}CO{\cdot}[CH_2]_4{\cdot}CH{:}CMe_2$
IV	$O{\cdot}C_6H_4{\cdot}NO_2(p)$, etc.	OMe	H	$CH_2{\cdot}NH{\cdot}CO{\cdot}C_6H_{11}$
V	OH	OMe	H	X
VI	OMe	OMe	H	X
VII	OH	OH	H	X
VIII	OMe	H	H	X
IX	OH	H	H	X
X	OH	OEt	H	X
XI	$O{\cdot}CH_2{\cdot}O$		H	X
XII	H	OMe	OH	X
XIII	OH	OMe	H	CH_2X
XIV	OH	OMe	H	$CH_2{\cdot}CHMe{\cdot}NH{\cdot}SO_2{\cdot}C_6H_4{\cdot}NH_2$

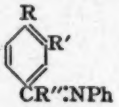
X = $\cdot CH_2{\cdot}NH{\cdot}SO_2{\cdot}C_6H_4{\cdot}NH_2(p)$.

The chaulmoogroyl *amide* was tested against tuberculosis in mice without result. The *p*-nitrobenzoates and other *esters* (IV) of the hexoyl amide were prepared; their reduced volatility decreased their sternutatory action, but their hot taste increased.

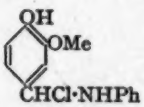
Sulphanilvanillylamide (V) had slight antimalarial activity against *P. gallinaceum* in chicks; accordingly, the *sulphanilbenzylamides* (VI), (VII), (VIII), (IX), (X), (XI), and (XII) were

prepared from the corresponding 4-aldehydes [except (IX), which was prepared from the amine (OH, H, H, $CH_2 \cdot NH_2$) obtained by demethylation of (OMe, H, H, $CH_2 \cdot NH_2$)]. None of these had greater activity than sulphanilvanillylamide. This is surprising in the case of (X) since the parent aldehyde (OH, OEt, H, CHO) has 20 times the taste of vanillin (OH, OMe, H, CHO). Since the corresponding N^1-phenylsulphanilamides which have been prepared do not show any great chemotherapeutical activity (Northey, *Chem. Reviews*, 1940, **27**, 97), the *homobenzylamide* (XIII) was prepared from homovanillin (Harries and Haarmann, *Ber.*, 1915, **48**, 29, 868), and the *compound* (XIV) from the corresponding amine supplied by Dr. J. H. Turnbull in the same way as the lower homologues. The results of the biological tests on these two compounds are not yet to hand.

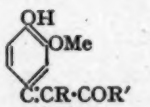
Piperonylideneaniline (XV; RR′ = O·CH_2·O, R″ = H) has been aminated with sodamide in toluene to give a 13% yield of the *amidine* (XV; RR′ = O·CH_2·O, R″ = NH_2) (Kirssanow and Iwastchenko, *Bull. Soc. chim.*, 1935, **2**, 2114, 2121). This method gave only a trace of the amidine (XV; R = OAc or OBz, R′ = OMe, R″ = NH_2) when applied to the vanillinanil derivatives (XV; R = OAc or OBz, R′ = OMe, R″ = H). Prolonged reaction with a solution of sodamide in liquid ammonia at room temperature gave a small yield of the *amidine* (XV; R = OAc, R′ = OMe, R″ = NH_2), which was condensed with *p*-acetylsulphanilyl chloride. The condensation product was hydrolysed under mild conditions with hydrochloric acid (Kwartler and Lucas, *J. Amer. Chem. Soc.*, 1943, **65**, 354) to give the *N-sulphanil-*N^1*-phenylamidine hydrochloride* (XV; R = OH R′ = OMe, R″ = NH·SO_2·C_6H_4·NH_2,HCl) which is undergoing biological tests.



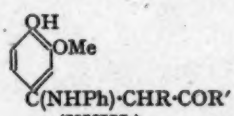
(XV.)



(XVI.)



(XVII.)



(XVIII.)

Vanillinanil was found to form a stable addition *compound* (XVI) with hydrogen chloride, on which ammonia or sodium hydroxide, under various conditions, either had no action or gave the free anil. With sodiocyanoacetic ester the compound gave (XVIII; R = CN, R′ = OEt), identical with the *product* of condensation of aniline and vanillylidenecyanoacetic ester, showing that the addition compound has the expected structure (XVI). The compounds (XVII) and (XVIII) (R = CN, R′ = OEt), under a modification of the conditions used by Pinner (*Ber.*, 1895, **28**, 478) for the conversion of cyanoacetic ester into α-amidinoacetamide hydrochloride, gave the *amidine hydrochlorides* (XVII) and (XVIII) [R = C(:NH)·NH_2,HCl, R′ = NH_2]. Poor yields were obtained in the former case owing to the low reactivity of the cyanide group, most of the starting material being recovered unchanged, and more drastic conditions decreased the yield; in the latter case much tar was formed, but less drastic conditions reduced the yield. The conversion of the ester into an amide took place when the imino-chloride was treated with alcoholic ammonia, and the use of more dilute ammonia to avoid this conversion gave a basic product which would not crystallise. In each case the free amidines were unstable oils which were not investigated further.

Experimental.

(All m. ps. and b. ps. are uncorrected.)

Preparation of Acyl Chlorides.—Thionyl chloride (1·5 equivs.) was added to a chloroform or ether solution of the acid (1 equiv.), the whole heated for 1 hr. on the water-bath, and the solvent and excess of thionyl chloride removed under reduced pressure; the unsaturated acid chlorides could not be distilled.

Preparation of Vanillylamides.—This was carried out as described by Nelson (*J. Amer. Chem. Soc.*, 1919, **41**, 2121) except that the amine was dried for 48 hrs. at 1 mm. in a vacuum desiccator. The hexoyl and undecenoyl vanillylamides agreed in every respect with the compounds described by Nelson (*ibid.*, pp. 2123, 2127).

Oleovanillylamide (cf. II).—Vanillylamine (1 g.) with oleoyl chloride (0·96 g.) gave the *amide* (0·9 g., 66%), which was recrystallised from benzene–petrol; m. p. 36° (Found: N, 3·4. $C_{26}H_{43}O_3N$ requires N, 3·4%).

Ricinoleovanillylamide.—Vanillylamine (1 g.) with ricinoleoyl chloride (1·1 g.) gave the *amide* (1·05 g., 65%), which crystallised from light petroleum (b. p. 40—60°) in colourless needles, m. p. 24° (Found: N, 3·7 $C_{35}H_{59}O_5N$ requires N, 3·5%).

Chaulmoogroyl Chloride.—Chaulmoogric acid (10 g.; m. p. 55°, equiv., 278) was dissolved in light petroleum (b. p. 40—60°, 100 c.c.), and phosphorus trichloride (3 g.) added dropwise with continuous stirring under anhydrous conditions at room temperature. The whole was gently refluxed with stirring for 0·4 hr. When cold, the light petroleum solution was decanted from the phosphoric acid, which

was washed by decantation with light petroleum. The volatile components were removed from the solution and washings under reduced pressure in a water-bath at 45°. The residue (10·6 g.) was used directly since it could not be distilled.

Chaulmoogrovanillylamide.—Vanillylamine (3·0 g. in ether as above) with chaulmoogroyl chloride (3·3 g.) gave the *amide* (3·4 g., 74%) as a colourless waxy solid, becoming cream on standing. Recrystallised from benzene–petrol, it had m. p. 69° (Found: C, 75·0; H, 10·0; N, 3·4. $C_{26}H_{41}O_3N$ requires C, 75·2; H, 9·9; N, 3·4%).

O-*Benzoyl*-N-*hexovanillylamide* (as IV).—To a mixture of benzoyl chloride (0·14 g.) and hexovanillylamide (0·25 g.) was added sodium hydroxide solution (25%) until no further reaction took place. After dilution, the *product* was filtered off; it recrystallised from toluene as a colourless crystalline solid (0·3 g., m. p. 210°) (Found: N, 4·0. $C_{21}H_{25}O_4N$ requires N, 3·95%).

O-p-*Nitrobenzoyl*-N-*hexovanillylamide.*—To *p*-nitrobenzoyl chloride (0·2 g.) in pyridine (2 c.c.) was added hexovanillylamine (0·25 g.). After being heated to 100° for 0·5 hr. and diluted with water, the *product* was collected; it crystallised from toluene in pale yellow needles (0·2 g.), m. p. 235° (Found: N, 7·4. $C_{21}H_{24}O_6N_2$ requires N, 7·0%).

O-2 : 4-*Dinitrobenzoyl*-N-*hexovanillylamide.*—Prepared as for the *p*-nitro-compound but from 2 : 4-dinitrobenzoyl chloride (0·24 g.), this *amide* crystallised from light petroleum (b. p. 100—120°) in yellow needles (0·3 g., m. p. 259°) (Found: N, 9·3. $C_{21}H_{23}O_8N_3$ requires N, 9·2%).

O-3 : 5-*Dinitrobenzoyl*-N-*hexovanillylamide.*—By a similar method, this *amide* was prepared; recrystallised from toluene, it formed yellow needles (0·25 g., m. p. 281°) (Found: N, 9·3%).

O-2 : 4 : 6-*Trinitrobenzoyl*-N-*hexovanillamide.*—Trinitrobenzoyl chloride (0·29 g.) in pyridine (1·4 c.c.) and hexovanillylamide (0·25 g.) were heated to 100° (for 0·25 hr.), the solution diluted, and the *product* recrystallised from toluene. It formed yellow needles (0·1 g., m. p. 296°) (Found: N, 11·7. $C_{21}H_{22}O_{10}N_4$ requires N, 11·45%).

O-5-*Nitrosalicyl*-N-*hexovanillylamide.*—Hexovanillylamide (0·25 g.) was added to 5-nitrosalicyl chloride (0·23 g.) in pyridine (2·2 c.c.) and allowed to stand. After dilution with water, the *product* was recrystallised from toluene, forming very pale yellow needles (0·24 g., m. p. 301°) (Found: N, 6·9. $C_{21}H_{24}O_7N_2$ requires N, 6·7%).

O-*Picryl*-N-*hexovanillylamide.*—Hexovanillylamide (0·25 g.) was added to picryl chloride, and the whole heated to 50° for 0·5 hr. The *product* was recrystallised from alcohol and then from methanol and formed yellow cubes (0·4 g., m. p. 149°) (Found: N, 8·4. $C_{20}H_{22}O_9N_4$ requires N, 8·3%).

The high m. ps. prevented successful volatilisation of the above compounds. The thoroughly dried, finely powdered materials were very irritating to the mucous membrane and had strong, hot tastes.

2-Chloro-5-nitrobenzenesulphonvanillylamide.—2-Chloro-5-nitrobenzenesulphonyl chloride (2·56 g.) was added to vanillylamine (1·5 g.) in acetone (25 c.c.) and pyridine (5 c.c.), and the whole warmed on the water-bath; after cooling, the *product* was filtered off and recrystallised with some difficulty from alcohol as colourless plates (3·0 g., m. p. 220°) (Found: N, 7·7. $C_{14}H_{13}O_6N_2SCl$ requires N, 7·6%).

Preparation of Oximes.—(1) Aldehydes with a free hydroxyl group (0·1 mol.) were dissolved in water (60 c.c.) containing sodium hydroxide (4·9 g.), and a solution of hydroxylamine hydrochloride (8·6 g.) in water (22 c.c.) was added. The whole was shaken until the precipitated oil solidified. After standing for 12 hrs. in the cold, the solid was filtered off and washed with water. The oximes could be purified with great loss by recrystallisation from toluene, but usually the crude product was used directly in the next stage.

(2) Aldehydes with no free hydroxyl group (0·1 mol.) were dissolved in alcohol (30—40 c.c.) and treated with hydroxylamine hydrochloride as above, followed by sodium hydroxide solution (10%, 45 c.c.) added in portions with shaking. After 3 hrs., a small amount of hydrochloric acid was added, and the precipitate filtered off and washed with water. The crude oxime was usually used directly in the next stage.

Preparation of Amine Hydrochlorides.—The oxime (0·1 mol.) was dissolved in alcohol (50 c.c.) and treated with sodium amalgam (4%, 250 g.) in small portions. The temperature was kept below 60°, and the mixture kept acid by gradual addition of glacial acetic acid (35—40 c.c.), then acidified to Congo-red with hydrochloric acid, and evaporated to dryness on the water-bath under reduced pressure. The residue was extracted with boiling alcohol, and on cooling, the amine hydrochloride crystallised out (*ca.* 0·05—0·06 mol.).

N^4-*Acetylsulphanilamides* (cf. Northey *et al.*, *J. Amer. Chem. Soc.*, 1938, **60**, 2220).—The amine hydrochloride (0·1 mol.) and water (100—120 c.c.) were efficiently stirred; sodium carbonate (6 g.) was added, followed alternately by *p*-acetamidobenzenesulphonyl chloride (24 g.; *Org. Synth.*, **5**, 3) and sodium hydroxide solution (40%; 7 c.c. for amines without a free hydroxyl group, 10—12 c.c. for those with) in small portions during 20 mins. The whole was stirred a further 20 mins., neutralised, and filtered. A small portion of the precipitate was recrystallised from alcohol or dilute alcohol and analysed.

Sulphanilamides.—The acetyl compound (0·1 mol.) was dissolved in aqueous or aqueous-alcoholic sodium hydroxide solution (8%; 120 c.c. for non-hydroxyl compounds, 160 c.c. for monohydroxy-, and 210 c.c. for dihydroxy-compounds) and heated on the water-bath for 2—3 hrs. The solution was filtered and made just acid to litmus with hydrochloric acid. The precipitate which separated on cooling was collected and dissolved in boiling water; active charcoal (2—3 g.) was added, and the whole refluxed for 10 mins. The solution was filtered, treated with a little ammonia, and then allowed to cool. The sulphanilamides separated in colourless or slightly sandy, well-formed crystals.

The hydrochlorides were obtained either by dissolving the free base in a small quantity of hot water and adding an excess of concentrated hydrochloric acid, or by dissolving the free base in hot alcohol and passing in hydrogen chloride until the solution was strongly acid. In both cases the hydrochlorides separated on cooling.

The m. ps. and analytical data of the compounds are shown in Tables II and III.

TABLE II.

Condensation products of benzylamines and N^4*-acetylsulphanilyl chloride.*

Amine.	Amine, HCl. M. p.	N^4-Acetyl sulphanil-amide. M. p.	Analysis. Found (%). C.	H.	Formula.	Required (%). C.	H.
Vanillylamine	decomp.	215°	54·9	5·1	$C_{16}H_{18}O_5N_2S$	54·9	5·1
Veratrylamine	257°	183	56·2	5·5	$C_{17}H_{20}O_5N_2S$	56·0	5·4
3 : 4-Dihydroxybenzylamine	172	175	52·1	4·3	$C_{15}H_{16}O_5N_2S$	52·2	4·35
p-Methoxybenzylamine	235	181—182	57·4	5·3	$C_{16}H_{18}O_4N_2S$	57·5	5·3
p-Hydroxybenzylamine	195 (HBr)	133	56·3	4·7	$C_{15}H_{16}O_4N_2S$	56·3	5·0
Vanillylethylamine	222—223	251 (decomp.)	55·9	5·1	$C_{17}H_{20}O_5N_2S$	56·0	5·4
Piperonylamine	227	181—182	55·4	4·4	$C_{16}H_{16}O_5N_2S$	55·2	4·6
O-Vanillylamine	decomp.	162	54·8	5·2	$C_{16}H_{18}O_5N_2S$	54·9	5·1

TABLE III.

Compound.	M. p.	*Free base.* Analysis. Found (%). C.	H.	Formula.	Required (%). C.	H.	M. p.	*Hydrochloride.* Analysis. Found (%). C.	H.	Required (%). C.	H.
V	*	54·6	5·3	$C_{16}H_{18}O_4N_2S$	54·5	5·2	*	48·8	4·95	48·9	5·0
VI	152—153°	56·2	5·7	$C_{15}H_{15}O_4N_2S$	55·9	5·6	210 *	50·6	5·2	50·2	5·3
VII	*	53·0	5·0	$C_{13}H_{14}O_4N_2S$	53·0	4·75	*	47·1	4·6	47·2	4·7
VIII	131	58·0	5·6	$C_{14}H_{16}O_3N_2S$	57·5	5·5	217	50·9	5·2	51·1	5·2
IX	*	54·0	4·8	$C_{13}H_{14}O_3N_2S$	54·2	4·9	213 *	48·3	4·4	48·1	4·6
X	*	55·7	5·4	$C_{15}H_{18}O_4N_2S$	55·9	5·6	*	50·4	5·3	50·2	5·3
XI	185—186	54·5	4·5	$C_{14}H_{14}O_4N_2S$	54·9	4·7	208—209	49·4	4·5	49·1	4·4
XII	163—164	54·8	5·7	$C_{14}H_{16}O_4N_2S$	54·5	5·2	193—194 *	49·2	5·2	48·9	5·0

* = Decomposes or melts with decomposition.

Sulphanilhomovanillylamide (XIII).—*O*-Acetylhomovanillin (Harries and Haarmann, *loc. cit.*; 20 g.) was refluxed with hydroxylamine hydrochloride (8 g.) and calcium carbonate (12 g.) in methanol (140 c.c.) with vigorous stirring for 3 hrs. The solution was filtered and treated as above with sodium amalgam (4%, 400 g.) and glacial acetic acid (65 c.c.). The O-*acetylhomovanillylamine hydrochloride* recrystallised from alcohol as colourless needles (9 g., m. p. 190° decomp.) (Found: C, 53·7; H, 6·6. $C_{11}H_{15}O_3N$,HCl requires C, 53·8; H, 6·5%). Condensation with acetylsulphanilyl chloride gave N^4-*acetylsulphanilhomovanillylamide* (11 g. crude) which crystallised from alcohol in stout prisms (m. p. 271° decomp.) (Found: C, 55·8; H, 5·1. $C_{17}H_{20}O_5N_2S$ requires C, 56·0; H, 5·4%). Hydrolysis with sodium hydroxide solution (10%, 100 c.c.) containing a little alcohol (5—6 c.c.) at 100° for 2 hrs. removed both acetyl groups to give *sulphanilhomovanillylamide*, which crystallised from water in colourless needles (6 g., m. p. 241° decomp.) (Found: C, 55·9; H, 5·5. $C_{15}H_{16}O_4N_2S$ requires C, 55·9; H, 5·6%). The *hydrochloride* (needles from alcohol) decomposed on heating (Found: C, 50·3; H, 5·6. $C_{15}H_{16}O_4N_2S$,HCl requires C, 50·2; H, 5·3%).

Sulphanil-α-vanillylethylamide. α-Vanillylethylamine (0·9 g., m. p. 157°) was condensed under the same conditions to give N^4-*acetylsulphanil-α-vanillylethylamide* (1·3 g., stout prisms from alcohol, m. p. 293°) (Found: C, 57·3; H, 5·8. $C_{19}H_{22}O_5N_2S$ requires C, 57·2; H, 5·8%). Hydrolysis with sodium hydroxide solution (10%, 5 c.c.) at 100° for 2 hrs. gave *sulphanil-α-vanillylethylamide* (0·9 g., needles from water, m. p. 252°) (Found: C, 57·1; H, 6·0. $C_{16}H_{20}O_4N_2S$ requires C, 57·2; H, 5·95%). The *hydrochloride* (long needles from alcohol) had m. p. 283° (Found: C, 52·9; H, 5·6. $C_{16}H_{20}O_4N_2S$,HCl requires C, 53·0; H, 5·8%).

Sulphanil-O-*acetylvanillylamide.*—Sulphanilvanillylamide sulphate (7·0 g.) and acetic anhydride (12 c.c.) were vigorously stirred while concentrated sulphuric acid (15 c.c.) was added drop-wise, the whole being maintained below 25°. Absolute alcohol was slowly added to the solution to a final volume of 130 c.c. The precipitate was filtered off, and the *amide sulphate* recrystallised from dilute sulphuric acid as colourless prisms (6·4 g.) (Found: C, 48·7; H, 4·8; N, 9·7. $C_{18}H_{18}O_4N_2,\frac{1}{2}H_2SO_4$ requires C, 48·8, H, 4·9; N, 9·7%). The compound gave no colour with ferric chloride but on diazotisation (Hodgson and Walker, *J.*, 1933, 1621) it coupled with alkaline β-naphthol to give a red product.

O-*Acetylvanillinanil.*—*O*-Acetylvanillin (9·7 g.) was refluxed with aniline (4·6 g.) in alcohol (50 c.c.) containing a trace of piperidine for 4 hrs. The alcohol was distilled off, and the residue poured into water. The precipitate was filtered off, washed with water, and recrystallised from dilute alcohol, forming glistening plates (13 g.), m. p. 85—86° (Found: C, 71·5; H, 5·7. $C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6%).

O-*Benzoylvanillinanil*, prepared as above from *O*-benzoylvanillin, or by a Schotten–Baumann benzoylation of vanillinanil, crystallised from dilute alcohol in glistening plates, m. p. 157—158° (Found: C, 76·1; H, 5·2. $C_{21}H_{17}O_3N$ requires C, 76·1; H, 5·1%).

O-*Acetylvanill*-N^1-*phenylamidine* (XV; R = OH, R′ = OMe, R″ = NH_2).—(1) Finely powdered sodamide (12 g.) was added to acetylvanillinanil (20 g.) in dry benzene (30 c.c.). The whole was stirred under anhydrous conditions and warmed in a bath at 85° (which was temporarily removed if frothing

became too violent) for 1 hr. Crushed ice (150 g.) was added to the cold pale green mass, the whole vigorously shaken, and acidified with dilute hydrochloric acid. The precipitate was filtered off and the filtrate boiled with a little active charcoal, refiltered, and evaporated to dryness. The residue was extracted with hot alcohol and the extract was concentrated, and the material deposited on cooling was recrystallised from alcohol, forming pale prisms (0·1 g.), m. p. 230° (decomp.). These were dissolved in a little water, and the solution basified and extracted with ether. The extract was dried, evaporated, and the residual *amidine* recrystallised from benzene–petrol, forming stout colourless prisms, m. p. 116° (Found: C, 67·1; H, 5·5. $C_{16}H_{16}O_2N_2$ requires C, 67·6; H, 5·6%).

(2) Powdered sodium (3 g.) was dissolved in liquid ammonia (200 c.c.) and acetylvanillinanil (10 g.) added. The whole was sealed in a stout tube and shaken at room temperature for 72 hrs. The ammonia was allowed to evaporate, a mixture of hydrochloric acid (25 c.c.) and crushed ice (150 g.) added, the whole shaken, and allowed to stand. The solution was filtered and evaporated to dryness, the residue extracted with hot alcohol, the alcohol removed, and the residue taken up in water (20 c.c.). The aqueous solution was boiled with a little active charcoal, filtered, and evaporated to dryness; the residue crystallised from alcohol in pale prisms (0·8 g.), m. p. 230° (decomp.), identical with the amidine hydrochloride above.

In both methods (1) and (2) the amidine was obtained directly by working up as described by Kirssanow and Iwastchenko (*locc. cit.*) and recrystallised from benzene–petrol; colourless plates, m. p. 119° [0·01 g. for method (1) and 0·2 g. for method (2)] (Found: C, 67·8; H, 5·6%).

O-*Benzoylvanill*-N^1-*phenylamidine*.—(1) Benzoylvanillinanil (22 g.), treated with sodamide as above, gave the amidine hydrochloride, which crystallised from alcohol in colourless plates (0·03 g.), m. p. 254° (decomp.). (2) Benzoylvanillinanil (11 g.) when aminated in liquid ammonia as above gave the *amidine hydrochloride* (0·9 g.), m. p. 245° (decomp.) (Found: C, 65·8; H, 4·4. $C_{21}H_{18}O_3N_2$,HCl requires C, 65·9; H, 4·6%).

The *amidine* was obtained by the alternative method of working up described above, or by dissolving the hydrochloride (0·5 g.) in water (4 c.c.), basifying the solution, and extracting it with ether. The extract was dried, the ether removed, and the residue recrystallised from benzene–petrol, forming colourless plates, m. p. 131° (Found: C, 71·0; H, 5·3. $C_{21}H_{18}O_3N_2$ requires C, 70·8; H, 5·05%).

N^4-*Acetylsulphanilyl*-O-*acetylvanill*-N^1-*phenylamidine*.—O-Acetylvanill-*N*^{1}-phenylamidine hydrochloride (0·5 g.) was dissolved in water, and sodium carbonate (0·2 g.) added, followed by *p*-acetamidosulphanilyl chloride (0·5 g.) and sodium hydroxide solution (10%, 0·8 g.) alternately in small portions at 40° with stirring. After 0·5 hr. the reaction mixture was allowed to cool, and the condensation *product* filtered off and recrystallised from alcohol (0·6 g. of colourless prisms, m. p. 180°) (Found: C, 59·1; H, 5·1. $C_{32}H_{32}O_6N_4S$ requires C, 58·8; H, 4·9%).

Sulphanilylvanill-N^1-*phenylamidine*.—The above diacetyl compound (0·5 g.) was suspended in alcoholic hydrogen chloride (20%, 20 c.c.) containing concentrated hydrochloric acid (0·5 c.c.). The whole was shaken at room temperature for 36 hrs., and the hydrochloride filtered off and recrystallised from dilute hydrochloric acid; stout needles (0·3 g., decomp. 222°) (Found: C, 55·4; H, 4·3. $C_{28}H_{19}O_4N_4S$,HCl requires C, 55·4; H, 4·4%). The hydrochloride was dissolved in water and the solution neutralised. The *amidine* was collected and recrystallised from dilute alcohol, forming colourless prisms, m. p. 150—152° (Found: C, 65·7; H, 5·0. $C_{28}H_{18}O_4N_4S$ requires C, 65·8; H, 5·1%).

Phenyl-α-chloro-4-hydroxy-3-methoxybenzylamine ("*Vanillinanil Hydrochloride*") (XVI).—(1) Vanillinanil (20 g.) was dissolved in hot alcohol (60 c.c.) and added to warm dilute hydrochloric acid (15%, 120 c.c.). On cooling, the solution gave large yellow cubes of the addition *compound* (20·5 g., m. p. 132°) (Found: Cl, 13·2. $C_{14}H_{14}O_2NCl$ requires Cl, 13·4%). (2) Vanillinanil (20 g.) was dissolved in warm alcohol (100 c.c.), and the solution saturated with hydrogen chloride at 50—60°. On cooling, small green crystals were formed (14 g., m. p. 206°) (Found: Cl, 13·3%). The yellow form was the more stable below 130°, and the green form the more stable above. If the yellow form was melted and the temperature of the bath maintained, the compound re-solidified to the green form; a mixture of the two forms softened slightly at 130°, but melted at 205°.

α-Amidinoacetamide Hydrochloride.—A mixture of cyanoacetic ester (10 g.) and alcohol (10 c.c.) was saturated at − 20° with dry hydrogen chloride, sealed in a stout tube, and kept at 40° for 30 hrs. The volatile components were removed in a vacuum, and the solid colourless residue shaken with ice-cold saturated alcoholic ammonia (250 c.c.). The solution was refluxed for 0·5 hr., concentrated, and filtered. The hot filtrate was acidified with hydrogen chloride and allowed to cool. The crystalline precipitate recrystallised from alcohol or water in colourless prisms (6 g., decomp. 162—163°) (Found: C, 26·6; H, 5·6. Calc. for $C_3H_8ON_3Cl$: C, 26·2; H, 5·8%).

α-Amidino-α-vanillylideneacetamide Hydrochloride [XVII; R = C(:NH)·NH$_2$, R′ = NH$_2$].—Vanillylidenecyanoacetic ester (Lapworth and Wykes, *J.*, 1917, **111**, 796; 8 g.) was dissolved in dry alcohol (160 c.c.) and saturated at − 20° with dry hydrogen chloride. The solution, sealed in a stout tube, was allowed to stand for 10 days. The volatile components were removed in a vacuum, and the residue shaken with cold saturated alcoholic ammonia (300 c.c.). After standing for 12 hrs., the solution was refluxed for 0·5 hr., concentrated, and filtered. The hot filtrate was acidified with hydrogen chloride and poured into cold water (500 c.c.). The whole was filtered, the filtrate refluxed with a little active charcoal, refiltered, and evaporated to dryness under reduced pressure on a water-bath. The residue was extracted with hot alcohol, the extract concentrated, and allowed to cool. The precipitate recrystallised from water in very pale green prisms (0·3 g., decomp. 151°) (Found: C, 45·5; H, 5·0. $C_{11}H_{13}O_3N_3$,HCl,H_2O requires C, 45·6; H, 5·2%).

Anilinovanillylcyanoacetic Ester (XVIII; R = CN, R′ = OEt).—(1) Cyanoacetic ester (3·5 g.) was refluxed with powdered sodium (0·4 g.) in pure dry benzene (50 c.c.) until no further reaction occurred. Vanillinanil hydrochloride (2 g.) was added in small portions with stirring, and the whole heated on the water-bath for 2·5 hrs. Water (100 c.c.) was added, the solution acidified, and extracted with ether. The extract was washed with water and dried (sodium sulphate), and the solvent removed. The residue recrystallised from dilute alcohol, giving yellow prisms (0·7 g., m. p. 101°) (Found: C, 67·0; H, 5·7. $C_{19}H_{20}O_4N_2$ requires C, 67·1; H, 5·9%).

(2) Vanillylidenecyanoacetic ester (10 g.) and aniline (6 g.) were sealed in a tube with a trace of piperidine acetate and heated at 100° for 48 hrs. The whole was poured into water and worked up as in (1), giving yellow prisms (3 g.), m. p. 101°.

β-Anilino-α-amidino-β-3-methoxy-4-hydroxyphenylpropionamide Hydrochloride [XVIII; R = C(:NH)·NH$_2$, R′ = NH$_2$].—The above ester (10 g.) was dissolved in a mixture of dry alcohol (5 c.c.) and dry dioxan (100 c.c.). The solution was saturated with dry hydrogen chloride at − 20° and kept for 20 days in a sealed tube. The volatile components were removed in a vacuum, and the residue shaken with cold saturated alcoholic ammonia (400 c.c.) and allowed to stand for 12 hrs. The solution was refluxed for 0·5 hr., concentrated, and filtered, and the hot filtrate acidified with hydrogen chloride. The whole was poured into water, filtered, the filtrate refluxed with a little active charcoal, and again filtered. The solution was evaporated to dryness under reduced pressure on the water-bath, the residue extracted with hot water, and the extract allowed to cool. The precipitated *amidine hydrochloride* was recrystallised from dilute alcohol, giving yellow prisms (1·2 g.), m. p. 135° (decomp.) (Found : C, 51·5; H, 6·1. $C_{17}H_{19}O_3N_4.HCl,2H_2O$ requires C, 51·1; H, 5·8%).

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KING'S COLLEGE, UNIVERSITY OF DURHAM,
NEWCASTLE-UPON-TYNE, 2.

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114. *The Cyano-ethylation of Arsines, and the Preparation of Amidino-alkyl-arsines and Carboxy-alkyl-arsines.*

By RICHARD C. COOKSON and FREDERICK G. MANN.

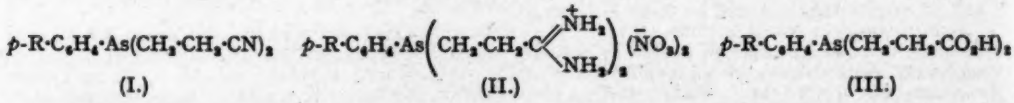
It is shown that primary and secondary arsines, of the type RAsH$_2$ and R$_2$AsH respectively, readily unite with vinyl cyanide to form 2-cyanoethyl-arsines of type AsR(CH$_2$·CH$_2$·CN)$_2$ and AsR$_2$·CH$_2$·CH$_2$·CN. 2-Cyanopropylene similarly gives 2-cyano-*n*-propyl-arsines. The cyanoethyl-arsines can be readily converted into the corresponding amidino-arsines, the therapeutic action of which is now being investigated. The 2-cyano-alkyl-arsines can also be readily hydrolysed to the corresponding 2-carboxy-alkyl-arsines.

Other more general methods for the synthesis of ω-carboxy-alkyl-arsines are discussed.

MANY examples of the direct union of vinyl cyanide with ammonia and with primary and secondary amines have been recorded. The cyanide reacts with ammonia, either liquid or in aqueous solution, to give a mixture of 2-cyanoethylamine, bis-2-cyanoethylamine and tris-2-cyanoethylamine, the proportion of these amines depending on the conditions (Hoffmann and Jacobi, D.R.-P. 598,185; Whitmore *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 725; Buc, Ford, and Wise, *ibid.*, 1945, **67**, 92; Wiedemann and Montgomery, *ibid.*, p. 1994). Primary amines similarly furnish the corresponding 2-cyanoethylamines, NHR·CH$_2$·CH$_2$·CN, and the bis-2-cyanoethylamines, NR(CH$_2$·CH$_2$·CN)$_2$, and secondary amines also give the 2-cyanoethylamines, NR^{1}R^2·CH$_2$·CH$_2$·CN (Hoffmann and Jacobi, *loc. cit.*; Roh and Wolff, D.R.-P. 641,597; Holcomb and Hamilton, *J. Amer. Chem. Soc.*, 1942, **64**, 1309; Whitmore *et al.*, *loc. cit.*); it is claimed that some of these reactions are reversible at high temperatures. Amides and imides unite similarly with vinyl cyanide (Wegler, D.R.-P. 734,725; 735,771; Galat, *J. Amer. Chem. Soc.*, 1945, **67**, 1414).

The union of vinyl cyanide with amines when sluggish has usually been promoted by the addition of basic catalysts such as sodium alkoxides, but acidic catalysts have occasionally been used. For example, Whitmore *et al.* (*loc. cit.*) have shown that neither carbazole nor tetrahydroquinoline will react with pure vinyl cyanide, but that the addition of benzyltrimethylammonium hydroxide to the carbazole or of glacial acetic acid to the tetrahydroquinoline induces the production of the 2-cyanoethyl derivative in high yield.

We have consequently investigated the interaction of vinyl cyanide with primary and secondary arsines. We find that phenylarsine, Ph·AsH$_2$, readily combines with vinyl cyanide to form the crystalline *phenylbis-2-cyanoethylarsine* (I, R = H). Gentle boiling, without the aid of catalysts, is sufficient to induce this combination, but addition of alkaline catalysts, such as a trace of aqueous potassium hydroxide or of sodium methoxide, makes the reaction



(I.) (II.) (III.)

exceedingly vigorous. This cyano-arsine, unlike the liquid aryldialkylarsines, does not apparently undergo oxidation even on long exposure to air. Otherwise it has the normal

properties of tertiary arsines; for example, with alkyl iodides it forms quaternary salts, and with potassium palladochloride it forms the crystalline non-ionic *dichlorodi(phenylbis-2-cyanoethylarsine)palladium*, $[Cl_2Pd\{Ph\cdot As(CH_2\cdot CH_2\cdot CN)_2\}_2]$.

This combination with vinyl cyanide appears to be general for primary arylarsines. Thus *p*-aminophenylarsine, $NH_2\cdot C_6H_4\cdot AsH_2$, similarly furnishes p-*aminophenylbis-2-cyanoethylarsine* (I, R = NH_2), which on acetylation gives the p-*acetamidophenyl* derivative (I, R = NHAc), and on treatment with aqueous potassium cyanate gives the p-*carbamido*-derivative (I, R = $NH\cdot CO\cdot NH_2$). The amino-group in (I, R = NH_2) has the normal properties of an aromatic amine: for example, the compound after diazotisation condenses with alkaline β-naphthol to form 2-*hydroxynaphthalene*-1-*azo*-p-*phenylbis-2-cyanoethylarsine*, $HO\cdot C_{10}H_6\cdot N_2\cdot C_6H_4\cdot As(CH_2\cdot CH_2\cdot CN)_2$.

The secondary aryl-arsine, diphenylarsine, Ph_2AsH, also combines with vinyl cyanide to form *diphenyl-2-cyanoethylarsine*, $Ph_2As\cdot CH_2\cdot CH_2\cdot CN$. 2-Cyanopropylene combines similarly with diphenylarsine to form diphenyl-2-cyano-*n*-propylarsine, $Ph_2As\cdot CH_2\cdot CHMe\cdot CN$, but this cyanide, unlike all the previous cyanides, could not be obtained crystalline, and has been identified only as crystalline derivatives.

These cyanoethyl-arsines have several interesting synthetic applications which we are now investigating. Thus the dicyanide (I, R = H), when treated with a mixture of alcohol and chloroform saturated with hydrogen chloride gives the crystalline but very deliquescent bis(imino-ether) hydrochloride, $Ph\cdot As[CH_2\cdot CH_2\cdot C(OEt):NH,HCl]_2$; this on subsequent treatment with ammonia forms the corresponding diamidine, which with nitric acid forms the highly crystalline, water-soluble *phenylbis-2-amidinoethylarsine dinitrate* (II, R = H). Other crystalline salts of this diamidine, such as the *dipicrate*, *disalicylate*, and *di*-3 : 5-*dinitrobenzoate*, have been isolated.

The *p*-acetamidophenyl *dinitrate* (II, R = NHAc), and the *p*-chlorophenyl *dinitrate* (II, R = Cl) have also been obtained crystalline, but the *p*-aminophenyl and the *p*-ureidophenyl compounds have been isolated solely as the *tripicrate* and *dipicrate* respectively. Diphenyl-2-cyanoethylarsine also furnished the crystalline *diphenyl-2-amidinoethylarsine nitrate*, $Ph_2As[CH_2\cdot CH_2\cdot C(\overset{+}{:}NH_2)NH_2]\overset{-}{N}O_3$.

The therapeutic activity of these arsine-amidines, which is now being examined, may prove of interest. It is known that diamidines and also certain 3-covalent arsenic derivatives have a beneficial effect on patients suffering from various forms of trypanosomiasis: whether the presence of both such groups in one molecule will stimulate, or completely suppress, such action has still to be determined. Arsenical amidines have been previously recorded only by Linsker and Bogert (*J. Amer. Chem. Soc.*, 1943, **65**, 932; 1944, **66**, 191) who prepared compounds such as $p\text{-}(HO)_2As\cdot C_6H_4\cdot C(\overset{+}{:}NH_2)\cdot NH_2,\overset{-}{C}l$ and $CN\cdot C_6H_4\cdot As:As\cdot C_6H_4\cdot C(\overset{+}{:}NH_2)\cdot NH_2,\overset{-}{C}l$, in all of which, however, the amidino-group was linked directly to the benzene ring.

Our dicyano-compounds also undergo ready alkaline hydrolysis. Thus *phenylbis-2-carboxyethylarsine* (III, R = H); the corresponding p-*chlorophenyl* compound (III, R = Cl), *diphenyl-2-carboxyethylarsine*, $Ph_2As\cdot CH_2\cdot CH_2\cdot CO_2H$, and *diphenyl-2-carboxy*-n-*propylarsine*, $Ph_2As\cdot CH_2\cdot CHMe\cdot CO_2H$, have been similarly prepared.

The acyl chlorides and esters of these acids, particularly of the dicarboxylic acids, offer a wide field of synthetic application. We are, for example, attempting to convert the acid (III, R = H) into its dicarboxylic chloride and then to cyclise this with aluminium chloride to the tricyclic diketo-arsine which would be analogous in general structure to the julolidine of von Braun, Heider, and Wyczatkowska (*Ber.*, 1918, **51**, 1215).

It is clear that the vinyl cyanide addition reaction can furnish ultimately only those alkylarsines which carry a 2-cyano- or 2-carboxy-group. We have consequently sought other reactions by which these groups can be introduced in any desired position in the alkyl radical. This can be readily achieved for the carboxylic acids, but not for the corresponding cyanides. For example, a mixture of phenyldichloroarsine (IV) and 1-bromo-3-cyanopropane, when refluxed with aqueous sodium hydroxide, yields ultimately *phenyl-3-carboxy*-n-*propylarsonic*

$$\underset{\text{(IV.)}}{Ph\cdot AsCl_2} \longrightarrow \underset{\text{(V.)}}{Ph\cdot AsO(OH)\cdot[CH_2]_3\cdot CO_2H} \longrightarrow \underset{\text{(VI.)}}{Ph\cdot AsCl\cdot[CH_2]_3\cdot CO_2H} \longrightarrow \underset{\text{(VII.)}}{Ph\cdot AsO([CH_2]_3\cdot CO_2H)_2}$$

$$\downarrow$$

$$\text{(VIII.)}\quad Ph\cdot As([CH_2]_3\cdot CO_2H)_2$$

acid (V), which when reduced with sulphur dioxide and hydrochloric acid gives *phenyl-3-carboxy*-n-*propylchloroarsine* (VI). This compound, when subjected to the original reaction, similarly furnishes *phenylbis-3-carboxy*-n-*propylarsine oxide* (VII), which is readily reduced to the tertiary

arsine (VIII). Similar reactions are given by 1-bromo-5-cyano-*n*-pentane. All attempts to convert the crystalline dicarboxy-arsine (VIII) into its esters or amide failed, however, and the corresponding dicyanide could not be prepared.

As an alternative attempt to prepare such cyano-arsines, phenyldimethylarsine was combined with 1-bromo-3-cyanopropane to form *phenyldimethyl-3-cyano-*n*-propylarsonium bromide*, $(AsPhMe_2 \cdot [CH_2]_3 \cdot CN)Br$. It was hoped that this compound on heating would dissociate to give methyl bromide and phenylmethyl-3-cyano-*n*-propylarsine, and the process could then be repeated with a second addition of the bromo-cyanide to give ultimately phenylbis-3-cyano-*n*-propylarsine. The above arsonium salt on heating, however, dissociated mainly into its two original components and the required tertiary cyano-arsine could not be obtained.

It is known that certain compounds containing ω-benzyloxyalkyl groups can be converted into the corresponding ω-hydroxyalkyl compounds even by the action of cold aqueous hydrobromic acid (Bennett, *J.*, 1925, **127**, 1279; Bennett and Hock, *J.*, 1927, 477). This indicated a method by which ω-hydroxyalkylarsines might be obtained and then converted through the chloro- into the ω-cyano-alkylarsines. Consequently, a mixture of phenyldichloroarsine and 2-benzyloxyethyl chloride $Ph \cdot CH_2 \cdot O \cdot [CH_2]_2 \cdot Cl$ was boiled in aqueous sodium hydroxide solution, and the crystalline *phenyl-2-benzyloxyethylarsonic* acid, $Ph \cdot AsO(OH) \cdot [CH_2]_2 \cdot O \cdot CH_2Ph$ thus obtained. All attempts to convert this by reduction into the chloroarsine, $PhAsCl \cdot [CH_2]_2 \cdot O \cdot CH_2Ph$, failed. As an alternative approach, phenyldichloroarsine was treated with 3-benzyloxypropylmagnesium chloride, and phenylbis-3-benzyloxypropylarsine, $PhAs([CH_2]_3 \cdot O \cdot CH_2Ph)_2$, obtained as an oil which could not be crystallised or distilled, and was identified as its *methiodide* and other crystalline derivatives. The benzyloxy-groups in this arsine proved to be firmly attached to the alkyl groups: the arsine was unaffected by boiling concentrated hydrochloric acid, and, although boiling hydrobromic acid appeared to give the desired action, the benzyl bromide thus formed apparently gave quaternary arsonium salts, and only intractable mixtures resulted. Furthermore, the arsine when heated with anhydrous pyridine hydrochloride gave only tarry products, although Prey (*Ber.*, 1941, **74**, 1219) has repeatedly used this reagent successfully for converting methoxyl into hydroxyl groups.

Experimental.

Unless otherwise stated, all the following compounds were colourless.

Preparation of Arsines.—(1) Phenylarsine, $PhAsH_2$, was prepared by the method of Palmer and Adams (*J. Amer. Chem. Soc.*, 1922, **44**, 1362).

(2) p-*Aminophenylarsine*, $NH_2 \cdot C_6H_4 \cdot AsH_2$. The preparation of this arsine has been briefly described (D.R.-P. 251,571) but without analytical data or statement of yield. Blicke and Oneto (*J. Amer. Chem. Soc.*, 1934, **56**, 686, footnote) state that their modifications of the preparation of this arsine will be described later, but these have not apparently yet been published.

Arsanilic acid (60 g.) and zinc dust (200 g.) were placed in a 2-l. flask fitted with the reflux condenser down which a stream of nitrogen was passed throughout the experiment. A solution of mercuric chloride (8 g.) in warm water (100 c.c.) was added with shaking, and then concentrated hydrochloric acid (600 c.c.) added dropwise during 12 hours, the mixture being periodically shaken. Crystalline plates of the hydrochloride or zincichloride of the arsine separated. The mixture was set aside, with occasional shaking, for 3 days. Excess of 20% aqueous sodium hydroxide was then added, and the liberated liquid arsine extracted with ether. The extract was separated, dried, and distilled (all these operations being carried out in an inert atmosphere), and the arsine was thus obtained as a colourless liquid, b. p. 84—92°/0·3 mm.; yield, 36 g. (77%). A drop of the arsine, exposed to the air in alcoholic solution, deposited yellow crystals of 4:4′-diaminoarsenobenzene, which, after recrystallisation from aqueous pyridine, had m. p. 224—226° (decomp., bath preheated to 215°) (Found: C, 43·4; H, 3·2; N, 8·7. Calc. for $C_{12}H_{12}N_2As_2$: C, 43·1; H, 3·6; N, 8·4). D.R.-P. 206,057 gives m. p. 139—141°: Ehrlich and Bertheim (*Ber.*, 1911, **44**, 1262) give m. p. 260°.

(3) p-*Chlorophenylarsine*, $Cl \cdot C_6H_4 \cdot AsH_2$. This was prepared essentially by the method employed for the previous arsine, but using methyl alcohol as a solvent during the reduction and omitting the final basification. It readily crystallised after distillation, b. p. 92°/14 mm.; yield, 38%. Palmer and Adams (*J. Amer. Chem. Soc.*, 1922, **44**, 1369) prepared the arsine by a similar reduction followed by steam distillation, and obtained a yield varying between 29 and 47%.

An ethereal solution of the arsine on exposure to air deposited crystals of *p*-chlorophenylarsonic acid, which were purified by dissolution in aqueous ammonia and reprecipitation with hydrochloric acid; m. p. 383—385° (decomp.) with previous loss of water (Found: C, 30·7; H, 2·4. Calc. for $C_6H_6O_3ClAs$: C, 30·4; H, 2·5%). Palmer and Adams (*loc. cit.*) give m. p. 348° (decomp.).

(4) *Diphenylarsine*, Ph_2AsH. Diphenylarsonic acid (100 g.) and zinc dust (160 g.), amalgamated by the addition of mercuric chloride (4 g.) in water (70 c.c.), were covered with ether (400 c.c.) under a nitrogen atmosphere, and concentrated hydrochloric acid (400 c.c.) was added dropwise down a reflux condenser to the shaken mixture. After 3 days the ethereal layer was forced by CO_2 pressure through a tube into a closed funnel, where it was dried, and thence into a large Claisen flask (also filled with CO_2), where it was distilled; b. p. 161—162°/20 mm., yield, 72 g. (82%). The large flask is necessary because of persistent foaming during distillation. Dehn and Wilcox (*Amer. Chem. J.*, 1906, **35**, 45), who record this arsine without preparative details or yield, give b. p. 174°/25 mm., 155°/37 mm., the latter being clearly in error.

Preparation of Dicyanides.—(1) *Phenylbis-2-cyanoethylarsine* (I, R = H). (i) A mixture of phenylarsine (13 g.) and vinyl cyanide (17 c.c., 3 mols.) was refluxed in a nitrogen atmosphere for 5 hours. The excess of vinyl cyanide was then distilled at atmospheric pressure, and the residue under reduced pressure; the *arsine* was thus isolated as a viscous liquid, b. p. 200—210°/0·1 mm. [18 g. (77%)], which ultimately solidified, and then, when recrystallised from ethanol–*cyclo*hexane, afforded needles, m. p. 59—60° (Found: C, 55·7; H, 4·9; N, 10·6; *M*, cryscopic in 0·636% ethylene dibromide solution, 261. $C_{12}H_{13}N_2As$ requires C, 55·4; H, 5·0; N, 10·8%; *M*, 260).

(ii) Crystallisation of the arsine may initially require several days: when once it occurs, however, larger preparations not involving distillation of the arsine may be carried out. For example, vinyl cyanide (80 c.c.) was added slowly to phenylarsine (42 g.) maintained at 70°, and the mixture then refluxed for 4 hours. The excess of vinyl cyanide was distilled, and the residue taken up in acetone. Cautious aqueous dilution of the acetone solution, with scratching and seeding, caused the deposition of the pure crystalline arsine; 56 g. (79%).

When the arsine was warmed with methyl iodide, a syrup resulted which could not be crystallised. When the syrup was treated with sodium picrate, both in aqueous alcohol, the *methopicrate* of the arsine was deposited as an oil which slowly crystallised, and then separated from benzene–acetone as yellow needles, m. p. 115—118·5° (Found: N, 14·0. $C_{19}H_{18}O_7N_5As$ requires N, 13·9%).

When the arsine (0·32 g.) in acetone (0·5 c.c.) was added to an agitated solution of ammonium palladochloride (0·17 g., 0·5 mol.) in aqueous alcohol (6 c.c.), *dichlorodi(phenylbis-2-cyanoethylarsine)-palladium* separated as an oil which later solidified, and then crystallised from aqueous acetone in fine brownish-yellow crystals, m. p. 189—195° (decomp.) (Found: C, 41·5; H, 3·6; N, 7·8. $C_{24}H_{26}N_4Cl_2As_2Pd$ requires C, 41·25; H, 3·7; N, 8·0%).

The *mercurichloride* was prepared by mixing alcoholic solutions of the arsine and mercuric chloride. The gum which was precipitated later crystallised, and separated from aqueous acetone in fine needles, m. p. 139—141° (Found: C, 27·25; H, 2·6; N, 5·3. $C_{12}H_{13}N_2As,HgCl_2$ requires C, 27·1; H, 2·4; N, 5·3%).

(2) p-*Aminophenylbis-2-cyanoethylarsine* (I, R = NH_2). Vinyl cyanide (35 c.c., 2·5 mols.) was added dropwise during 1 hour to *p*-aminophenylarsine (35·7 g.) maintained at 55° in a nitrogen atmosphere and occasionally shaken. The mixture was then heated at 100° for 4 hours, and the excess of vinyl cyanide then distilled. The residual *arsine* when cooled and scratched solidified (55·6 g., 96%), and when recrystallised from ethyl alcohol–ethyl acetate and then from alcohol afforded needles, m. p. 77·5—78·5° (Found: C, 52·6; H, 5·0; N, 15·2. $C_{12}H_{14}N_3As$ requires C, 52·35; H, 5·1; N, 15·3%).

When a solution of this arsine in acetic acid–acetic anhydride was refluxed for 30 minutes and then poured into water, the p-*acetamidophenyl* derivative (I, R = NHAc) was deposited as an oil which rapidly solidified; crystallisation from aqueous acetone or acetone–*cyclo*hexane afforded crystals, m. p. 117—118·5° (Found: C, 53·3; H, 5·2; N, 13·2. $C_{14}H_{16}ON_3As$ requires C, 53·0; H, 5·05; N, 13·2%).

When chloroacetyl chloride (1 c.c., 1·8 mols.) was added dropwise to an agitated suspension of the arsine (I, R = NH_2) (2 g.) in water (6 c.c.) containing sodium carbonate (0·8 g., 1 mol.), the p-*chloroacetamidophenyl* derivative (I, R = NH·CO·CH_2Cl) separated. After 1 hour, this was collected (2·3 g., 90% of the theoretical) and recrystallised first from ethyl acetate–*cyclo*hexane and then from alcohol; m. p. 96° (Found: C, 47·7; H, 4·2; N, 12·0. $C_{14}H_{15}ON_3ClAs$ requires C, 47·8; H, 4·3; N, 11·9%).

When solutions of the arsine (I, R = NH_2) (5 g.) in N-hydrochloric acid (18·2 c.c., 1 mol. acid) and of sodium cyanate (1·2 g., 1 mol.) in water (15 c.c.) were mixed, the p-*carbamidophenyl* derivative (I, R = NH·CO·NH_2) was immediately precipitated as an oil which slowly solidified [5·8 g. (100%)]. Recrystallisation from aqueous alcohol and then from alcohol alone gave needles, m. p. 142—147° (Found: C, 49·4; H, 5·1; N, 17·7. $C_{13}H_{15}ON_4As$ requires C, 49·1; H, 4·7; N, 17·6%).

When a solution of the arsine (I, R = NH_2) in hydrochloric acid was diazotised and then added to an alkaline solution of β-naphthol, the deep red 2-*hydroxynaphthalene*-1-*azo*-p-*phenylbis*-2-*cyanoethylarsine* was immediately precipitated, but required crystallisation from aqueous pyridine, aqueous acetic acid, and alcohol in turn for purification; m. p. 86—90° after heating at 65°/0·1 mm. (Found: C, 61·9; H, 4·0; N, 12·7. $C_{32}H_{19}ON_4As$ requires C, 61·7; H, 4·4; N, 12·6%).

(3) p-*Chlorophenylbis-2-cyanoethylarsine* (I, R = Cl). *p*-Chlorophenylarsine (14·6 g.) and vinyl cyanide (5 c.c.) were heated slowly to 90°, more cyanide (10 c.c.) then slowly added, and the whole finally refluxed for 2 hours. The cold product was poured into water. The *arsine* separated and rapidly crystallised; 21 g. (92%). Recrystallisation from aqueous alcohol gave needles, m. p. 71—72° (Found: C, 48·8; H, 4·1; N, 9·3. $C_{12}H_{12}N_2ClAs$ requires C, 48·9; H, 4·1; N, 9·5%).

This arsine was characterised by conversion into *dichlorodi*-(p-*chlorophenylbis*-2-*cyanoethylarsine*)-*palladium*, yellow needles from aqueous acetone, m. p. 160—163° (decomp.) (Found: C, 37·6; H, 3·1; N, 6·9. $C_{24}H_{24}N_4Cl_4As_2Pd$ requires C, 37·5; H, 3·1; N, 7·3%).

Diphenyl-2-cyanoethylarsine.—When diphenylarsine and vinyl cyanide (1·25 mols.) were refluxed for 1·5 hours in a nitrogen atmosphere, and the excess of vinyl cyanide then removed, the residue consisted of the liquid cyano-arsine contaminated with crystalline tetraphenyldiarsine, $Ph_2As{\cdot}AsPh_2$. A small portion of the crude residue was heated at 0·6 mm.; the distillate of cyano-arsine then solidified on cooling. The main bulk of crude product, dissolved in alcohol, was therefore filtered to remove the diarsine, and then, when mixed with water and seeded, gave the solid *diphenyl-2-cyanoethylarsine* (83%), which was crystallised further from *cyclo*hexane and then from aqueous alcohol, the product being collected in a chilled filter; needles, m. p. 37—39° (Found: C, 63·5; H, 4·6; N, 5·0. $C_{15}H_{14}NAs$ requires C, 63·65; H, 4·95; N, 4·95%).

The crystals of tetraphenyldiarsine were stable whilst under alcohol, but on exposure to air fused with much heat generation (cf. Borgstrom and Dewar, *J. Amer. Chem. Soc.*, 1922, **44**, 2917). For identification, their alcoholic suspension was treated with alcoholic iodine until conversion into diphenyliodoarsine was complete, and the latter then treated in turn with piperidine *N*-pentamethylenedithiocarbamate. The precipitated crystals of *N*-pentamethylene-*S*-diphenylarsinodithiourethane, when recrystallised from

ethyl acetate, had m. p. 109·5—110°, unchanged by an authentic specimen prepared from diphenylchloroarsine. Blicke and Oakdale (*J. Amer. Chem. Soc.*, 1932, **54**, 2993) give m. p. 114—115°. The diarsine must have arisen in our experiments by slight atmospheric oxidation in spite of the precautions taken.

*Diphenyl-2-cyano-*n*-propylarsine*, $Ph_2As{\cdot}CH_2{\cdot}CHMe{\cdot}CN$.—A mixture of diphenylarsine (7·8 g.) and 2-cyanopropylene (3·6 c.c., 1·25 mols.) was refluxed for 4 hours in a nitrogen atmosphere. The cold viscous product was dissolved in alcohol and a small quantity of tetraphenyldiarsine removed by filtration. Aqueous dilution of the filtrate reprecipitated the oily cyano-compound, which could not be obtained solid, even when a small portion was distilled at 2 mm. (bath temperature 280—290°). The following derivatives were prepared:

(*a*) An alcoholic solution of the viscous distillate, shaken with aqueous potassium palladochloride, furnished *dichlorobis(diphenyl-2-cyano-*n*-propylarsine)palladium*, yellowish-brown crystals, m. p. 172—174° (decomp.) after crystallisation from aqueous acetone (Found: N, 3·5. $C_{32}H_{32}N_2Cl_2As_2Pd$ requires N, 3·6%).

(*b*) Another portion of the distillate was warmed with methyl iodide and then set aside for 1 day. The residual viscous syrup, dissolved in alcohol and treated with alcoholic sodium picrate, deposited *diphenylmethyl-2-cyano-*n*-propylarsonium picrate*, yellow needles from aqueous alcohol, m. p. 125—129° (Found: C, 51·6; H, 3·9; N, 10·3. $C_{33}H_{31}O_7N_4As$ requires C, 51·1; H, 3·9; N, 10·4%).

(*c*) The hydrolysis of the cyanide to the crystalline acid is described later.

Preparation of Amidino-compounds.—(1) *Phenylbis-2-amidinoethylarsine.* A solution of the dicyanide (I, R = H) (3·6 g.) in alcohol (4·5 c.c., 5·5 mols.) and chloroform (20 c.c.) was saturated with dry hydrogen chloride at 0°, and then set aside in a stoppered flask at room temperature for 4 days. Removal of the solvent at 18 mm. followed by very gentle warming gave a syrup which rapidly crystallised. This bis(iminoether) hydrochloride was highly deliquescent and was not purified. Saturated alcoholic ammonia (60 c.c.) was added with shaking, and the clear solution set aside for 5 days. The solvent was then evaporated at 18 mm. (with intermediate filtration of the precipitated ammonium chloride); the residual diamidine dihydrochloride formed a froth-like glass which was also very deliquescent. Consequently it was dissolved in water and treated with saturated sodium nitrate solution. The *diamidine dinitrate monohydrate* (II) separated as an oil which ultimately solidified, and was then recrystallised from alcohol–*cyclo*hexane; needles, m. p. 156—157° (Found: C, 33·4; H, 4·8; N, 19·2. $C_{12}H_{19}N_4As,2HNO_3,H_2O$ requires C, 32·9; H, 5·25; N, 19·2%); 4·2 g. (69%).

The amidine nitrate was hydrolysed by boiling 15% aqueous potassium hydroxide solution, and the arsinedicarboxylic acid (III) isolated, m. p. 83—85°, unchanged by admixture with an authentic specimen (see later), showing that it was the hydrated arsine, $PhAsR_2,H_2O$, and not the anhydrous arsine oxide, $PhAsR_2O$, which might have been formed by oxidation of the tertrary arsine by nitric acid, and could not have been definitely distinguished by the analyses only.

The following salts of the diamidine were prepared by treating a concentrated aqueous solution of the crude dihydrochloride with the sodium salt of the appropriate acid. *Dipicrate*, orange-yellow crystals from aqueous acetone, m. p. 189—190° (decomp., bath preheated to 180°) (Found: N, 18·9. $C_{12}H_{19}N_4As,2C_6H_3O_7N_3$ requires N, 18·6%). *Disalicylate monohydrate*, crystals from water, m. p. 98·5—103·5° (Found: C, 53·45; H, 5·6; N, 9·2. $C_{12}H_{19}N_4As,2C_7H_6O_3,H_2O$ requires C, 53·1; H, 5·6; N, 9·5%). *Bis-3:5-dinitrobenzoate*, very pale yellow needles from water, m. p. 90—105° (unchanged by repeated recrystallisation) (Found: C, 43·5; H, 3·8; N, 15·6. $C_{12}H_{19}N_4As,2C_7H_4O_6N_2$ requires C, 43·4; H, 3·8; N, 15·6%).

(2) p-*Aminophenylbis-2-amidinoethylarsine* (as II, R = NH_2). Prepared precisely as the previous diamidine, except that the chloroform solution in the first stage formed two layers. The crude diamidine dihydrochloride again formed a very deliquescent sticky glass, and the only crystalline salt isolated was the *tripicrate*, yellow crystals from water, m. p. 138° (decomp.) after drying at 100°/0·1 mm. (Found: C, 36·05; H, 3·2; N, 19·4. $C_{12}H_{20}N_5As,3C_6H_3O_7N_3$ requires C, 36·15; H, 2·9; N, 19·7%).

(3) p-*Acetamidophenyl-diamidine* (as II, R = NHAc). (i) The crude diamidine dihydrochloride obtained in the previous experiment was boiled with acetic acid–acetic anhydride for 20 minutes, and then evaporated under reduced pressure. An aqueous solution of the residue when treated (*a*) with sodium nitrate solution gave the *diamidine dinitrate monohydrate*, m. p. 136° (efferv. with preliminary softening) after repeated crystallisation from alcohol–*cyclo*hexane (Found: C, 34·3; H, 5·5; N, 19·7. $C_{14}H_{22}ON_5As,2HNO_3,H_2O$ requires C, 33·9; H, 5·25; N, 19·8%); (*b*) with sodium 3:5-dinitrobenzoate gave the *diamidine bis-3:5-dinitrobenzoate dihydrate*, pale yellow microcrystalline powder from water, m. p. indefinite (115—155°) (Found: C, 41·4; H, 4·1; N, 15·8. $C_{14}H_{22}ON_5As,2C_7H_4O_6N_2,2H_2O$ requires C, 41·45; H, 4·2; N, 15·5%).

(ii) *p*-Acetamidophenylbis-2-cyanoethylarsine (I, R = NHAc) was converted into the diamidine dihydrochloride in the usual way and then precipitated as the dinitrate monohydrate (92% yield), identical with that formed in (i).

(4) p-*Carbamidophenyl-diamidine* (as II, R = NH·CO·NH_2). Prepared in the usual way from the dicyanide (I, R = NH·CO·NH_2), and finally precipitated as the *dipicrate monohydrate*, orange crystals from water, m. p. 118—120° (Found: C, 35·6; H, 3·5; N, 20·4. $C_{13}H_{21}ON_6As,2C_6H_3O_7N_3,H_2O$ requires C, 36·2; H, 3·5; N, 20·3%).

(5) p-*Chlorophenyl-diamidine* (as II, R = Cl). Prepared in the usual way. *Dinitrate monoalcoholate*, plates from alcohol, m. p. 103—105° (Found: C, 33·2; H, 5·2; N, 17·0. $C_{12}H_{18}N_4ClAs,2HNO_3,C_2H_6O$ requires C, 33·5; H, 5·2; N, 16·8%); *dipicrate monohydrate*, yellow crystals from aqueous alcohol, m. p. 202° (decomp.) (Found: C, 37·0; H, 3·1; N, 17·9. $C_{12}H_{18}N_4ClAs,2C_6H_3O_7N_3,H_2O$ requires C, 37·3; H, 3·4; N, 18·1%).

(6) *Diphenyl-2-amidinoethylarsine.* Prepared as before. *Nitrate hemihydrate*, needles from alcohol, m. p. 162—164° (decomp.) (Found: C, 48·3; H, 4·9; N, 11·5. $C_{15}H_{17}N_3As,HNO_3,\frac{1}{2}H_2O$ requires C, 48·35; H, 5·1; N, 11·3%); *picrate*, yellow needles from alcohol, m. p. 193—195° (decomp.) (Found: C, 48·0; H, 4·0; N, 13·15. $C_{15}H_{17}N_3As,C_6H_3O_7N_3$ requires C, 47·6; H, 3·8; N, 13·2%).

Preparation of Arsine-carboxylic Acids.—(1) *Phenylbis-2-carboxyethylarsine* (III, R = H). The

dicyanide (I, R = H) (25 g.) was added to a solution of potassium hydroxide (22 g., 4 mols.) in 50% aqueous alcohol (120 c.c.), refluxed for 4 hours, and the alcohol then distilled off. The residual solution, when cooled, diluted, and acidified, deposited the above *acid* as an oil which slowly crystallised; needles from chloroform–*cyclo*hexane, m. p. 83—84·5° (Found: C, 48·6; H, 4·9. $C_{12}H_{15}O_4As$ requires C, 48·3; H, 5·0%); 24 g. (84%).

(2) p-*Chlorophenylbis-2-carboxyethylarsine* (III, R = Cl). This *acid*, similarly prepared from the dicyanide, formed needles from aqueous alcohol, m. p. 67—69° (Found: C, 43·6; H, 4·4. $C_{12}H_{14}O_4ClAs$ requires C, 43·3; H, 4·2%).

(3) *Diphenyl-2-carboxyethylarsine*, similarly prepared, formed crystals from aqueous alcohol, m. p. 104—106° (Found: C, 59·3; H, 5·1. $C_{16}H_{15}O_2As$ requires C, 59·6; H, 5·0%).

(4) *Diphenyl-2-carboxy-*n*-propylarsine*, similarly prepared from the crude syrupy cyanide, was precipitated on acidification initially as an oil which slowly crystallised; m. p. 82° after crystallisation from aqueous acetic acid and then from alcohol (Found: C, 60·5; H, 5·45. $C_{16}H_{17}O_2As$ requires C, 60·7; H, 5·4%).

3-Cyanopropyl Derivatives.—A mixture of phenyldichloroarsine (IV) (164 g.) and 1-bromo-3-cyanopropane (120 g., 1·1 mols.) was added slowly with stirring to 40% aqueous sodium hydroxide solution (444 c.c., 6 mols. NaOH) and then refluxed for 6 hours. The cold product was just acidified with hydrochloric acid (phenolphthalein), filtered to remove sodium halide and phenylarsine oxide, and then acidified to Congo-red. The precipitated *phenyl-3-carboxy-*n*-propylarsonic acid* (V) (177 g., 89%) was collected and recrystallised from water or alcohol; needles, m. p. 143—145·5° (Found: C, 44·2; H, 4·8. $C_{10}H_{13}O_4As$ requires C, 44·1; H, 4·8%).

Sulphur dioxide was passed into a solution of this arsonic acid (99 g.) in concentrated hydrochloric acid (150 c.c.) containing potassium iodide (0·1 g.) until no more solid separated. The crystalline *phenyl-3-carboxy-*n*-propylchloroarsine* (VI) (88 g., 88%) was collected and recrystallised from light petroleum (b. p. 100—120°); needles, m. p. 45° (Found: C, 44·1; H, 4·5; Cl, 12·9. $C_{10}H_{12}O_2ClAs$ requires C, 43·7; H, 4·4; Cl, 12·9%). The first preparation of this compound gave an oil which did not crystallise for many days; in subsequent preparations, therefore, the hydrochloric acid was seeded with the crystalline chloroarsine before reduction, which then proceeded as described above. This is important, because attempts to purify the oily chloroarsine by distillation under reduced pressure caused decomposition and loss of hydrogen chloride.

A mixture of the chloroarsine (VI) (159 g.) and 1-bromo-3-cyanopropane (94 g., 1·1 mols.) was slowly added to 40% sodium hydroxide solution (350 c.c., 6 mols. NaOH), and the preparation continued as described above. Acidification finally to Congo-red precipitated a pasty mass which was collected, and an oily impurity extracted with acetone, leaving the pure crystalline *phenylbis-3-carboxy-*n*-propylarsine oxide* (VII), m. p. 133—136°, unchanged by recrystallisation from benzene–methyl alcohol (Found: C, 49·5; H, 5·5. $C_{14}H_{19}O_5As$ requires C, 49·1; H, 5·7%); 124 g. (63%). A portion of the oxide, dissolved in cold concentrated hydrochloric acid, rapidly deposited deliquescent crystals of the tertiary *arsine dichloride*, m. p. 152° (Found: Cl, 17·9. $C_{14}H_{19}O_4Cl_2As$ requires Cl, 17·9%).

A suspension of the arsine oxide (VII) (60 g.) in chloroform (110 c.c.) mixed with concentrated hydrochloric acid (2 c.c.) and water (15 c.c.) was saturated with sulphur dioxide. The chloroform layer was separated and diluted with light petroleum (b. p. 80—100°), whereby *phenylbis-3-carboxy-*n*-propylarsine* (VIII) was precipitated, m. p. 71—74° (Found: C, 51·2; H, 6·1. $C_{14}H_{19}O_4As$ requires C, 51·5; H, 5·8%). A portion of the arsine was dissolved in aqueous ammonia and evaporated to dryness; an aqueous solution of the residue when treated with silver nitrate gave the white microcrystalline *disilver* salt (Found: C, 31·6; H, 3·3. $C_{14}H_{17}O_4AsAg_2$ requires C, 31·2; H, 3·2%).

When a mixture of the dichloroarsine (IV) (23·1 g.) and 1-bromo-5-cyanopentane, b. p. 132°/13 mm. (20 g.), was added to 40% sodium hydroxide (62 c.c.), and the experiment continued as above, *phenyl-5-carboxy-*n*-pentanearsonic acid* was obtained, colourless crystals from diethyl carbonate, m. p. 101·5—103° (Found: C, 48·2; H, 6·0. $C_{12}H_{17}O_4As$ requires C, 48·0; H, 5·7%).

Quaternary Arsonium Bromides.—A mixture of phenyldimethylarsine (51·9 g.) and 1-bromo-3-cyanopropane (42·2 g., 1 mol.) was heated at 120° for 4 hours in a nitrogen atmosphere. The cold solid product, recrystallised from alcohol, gave *phenyldimethyl-3-cyanopropylarsonium bromide*, m. p. 170° (Found: C, 43·6; H, 5·2; N, 4·2. $C_{12}H_{17}NBrAs$ requires C, 43·6; H, 5·2; N, 4·2%); 72 g. (77%). An aqueous solution of the bromide, treated with sodium picrate, gave the *arsonium picrate*, orange-yellow plates from aqueous alcohol, m. p. 119° (Found: N, 11·8. $C_{18}H_{19}O_7N_4As$ requires N, 11·7%).

The arsonium bromide (72 g.) was heated under reduced pressure and three arbitrary fractions collected: (*a*) b. p. rising to 139°/20 mm., 16 g.; (*b*) b. p. 139—150°/20 mm. 16 g.; (*c*) b. p. rising to 130°/0·2 mm., 16 g. Fraction (*a*) when set aside very slowly deposited the original crystalline bromide in small amount. Fraction (*b*) also deposited this bromide (5 g.), but also contained phenyldimethylarsine, since with methyl iodide it readily gave phenyltrimethylarsonium iodide, colourless crystals from alcohol–ether, m. p. 248° unaffected by admixture with an authentic specimen (Burrows and Turner, *J.*, 1920, **117**, 1378, give m. p. 250°), and this iodide in turn furnished the arsonium picrate, m. p. 144° (Steinkopf and Schwen, *Ber.*, 1921, **54**, 1448, give m. p. 145°). Fraction (*c*) on refractionation gave 3 fractions: (i) b. p. 60—71°/1·2 mm. (2·4 g.), which formed an almost solid mass of the original bromide; (ii) b. p. 70—72°/1·5 mm. (3·3 g.); (iii) b. p. 72°/1·5 mm.—120°/0·1 mm. (6·1 g.). Fractions (ii) and (iii) also contained much arsonium bromide, but remaind liquid. It was clear therefore that the arsonium bromide on heating was dissociating mainly to phenyldimethylarsine and 1-bromo-3-cyanopropane, and that these products were recombining in the distilled material.

A mixture of phenyldimethylarsine (9·7 g.) and 1-bromo-5-cyano-*n*-pentane (9·4 g., 1 mol.), when heated under a CO_2-atmosphere in a sealed tube at 100° for 60 hours, first separated into two layers and ultimately again became homogeneous. The cold viscous product when scratched formed a deliquescent crystalline mass of phenyldimethyl-5-cyano-*n*-pentylarsonium bromide, which was identified as the *picrate*, yellow needles from aqueous alcohol, m. p. 58—59° (Found: N, 10·9. $C_{20}H_{23}O_7N_4As$ requires N, 11·1%). When the anhydrous bromide was heated, however, only phenyldimethylarsine was detected in the distillate, and this bromide also was therefore dissociating into its original components.

Both the above arsonium bromides were converted to the corresponding arsonium hydroxides, but these when heated gave no products that could be readily identified.

Attempts to condense either of the above bromoalkyl cyanides with the arsenic halides or with phenyldichloroarsine by the action of sodium in ether gave none of the desired tertiary cyanoarsines.

Benzyloxy-derivatives.—A mixture of phenyldichloroarsine (143 g.) and 2-benzyloxyethyl chloride (120 g., 1·1 mols.) was run slowly with stirring into 40% aqueous sodium hydroxide solution (420 c.c., 6 mols. NaOH) and the whole refluxed for 7 hours. The cold product formed two layers, the lower containing much crystalline sodium salt of the required arsonic acid (see later). Water was added until this salt dissolved, the mixture was then twice extracted with ether, and the aqueous layer then treated with concentrated hydrochloric acid until cloudy, filtered to remove sodium chloride, and then just acidified with more acid. Crystalline *phenyl-2-benzyloxyethylarsonic acid* (168 g., 82%) separated, and was collected and recrystallised from dilute methyl alcohol, m. p. 109° (Found: C, 56·6; H, 5·2. $C_{15}H_{17}O_3As$ requires C, 56·25; H, 5·3%). A small portion of the sodium salt, removed for identification and recrystallised from acetone containing a trace of water, gave the *trihydrate*, plates, m. p. 77°, resolidifying and then remelting at 248° (decomp.) (Found: C, 45·9; H, 6·1. $C_{15}H_{16}O_3AsNa,3H_2O$ requires C, 45·5; H, 5·6%); drying at 120°/20 mm. gave the hygroscopic anhydrous *salt*, m. p. 249° (decomp.) (Found: C, 53·0; H, 4·8. $C_{15}H_{16}O_3AsNa$ requires C, 52·6; H, 4·7%). The addition of concentrated hydrochloric acid to the arsonic acid or its sodium salt gave an oil which crystallised on scratching, and when recrystallised from benzene or ethyl carbonate gave the *arsonic acid hydrochloride*, $RR'As(OH)_2Cl$, plates, m. p. 94° (Found: C, 50·65; H, 5·1; Cl, 9·55. $C_{15}H_{18}O_3ClAs$ requires C, 50·5; H, 5·05; Cl, 10·0%). The prolonged action of sulphur dioxide on the arsonic acid in cold concentrated hydrochloric acid gave only the above unchanged arsonic acid hydrochloride; at 100° an oil was formed which could not be crystallised or distilled, and yielded no crystalline derivatives.

A Grignard reagent was prepared by the action of 3-benzyloxypropyl chloride (40 g., 2 mols.) in ether (120 c.c.) on specially activated magnesium (5·53 g.) under a nitrogen atmosphere, the reaction being initiated by the addition of ethyl bromide (0·2 c.c.) and bromine (1 drop) and local warming. The product was refluxed for 1 hour to complete the formation of the reagent, and then cooled in ice and stirred whilst a solution of phenyldichloroarsine (21·7 g., 0·9 mol.) in light petroleum (b. p. 40—60°, 100 c.c.) was slowly added. After a further 2 hours' refluxing, the white cloudy mixture was cooled and hydrolysed by the addition of ammonium chloride (25 g.) dissolved in water (150 c.c.). The upper layer was then separated and dried, and the organic solvents were removed. The residual oily colourless arsine (40 g.) could not be distilled. It was identified by the formation of the following derivatives: (i) An aqueous solution of the arsine, treated with aqueous ammonium chloropalladite, deposited an oil which ultimately solidified and when recrystallised from alcohol afforded golden-yellow plates of *dichlorobis(phenylbis-3-benzyloxypropylarsine)palladium*, m. p. 69° (Found: C, 57·9; H, 5·7. $C_{52}H_{62}O_4Cl_2As_2Pd$ requires C, 57·9; H, 5·75%). (ii) The arsine reacted with warm methyl iodide to form an oil which crystallised when stirred with ether; reprecipitation from acetone solution by the addition of ether gave *phenylmethylbis-3-benzyloxypropylarsonium iodide*, m. p. 67—69·5° (Found: C, 55·1; H, 6·1; I, 21·8. $C_{27}H_{34}O_3AsI$ requires C, 54·7; H, 5·7; I, 21·45%). (iii) The arsine combined with hot benzyl bromide to give a viscous oil, which, treated in alcoholic solution with chloroplatinic acid, gave *phenylbenzylbis-3-benzyloxypropylarsonium chloroplatinate*, pinkish-yellow crystals from alcohol–acetone, m. p. 119·5—121° (Found: C, 52·9; H, 5·15. $C_{44}H_{76}O_4Cl_6As_2Pt$ requires C, 52·9; H, 5·1%). The almost quantitative yield of the last two products indicated the purity of the tertiary arsine. No crystalline oxide or oxide-salts of the arsine could be isolated. The arsine was debenzylated by hydrobromic acid (constant b. p.) at 90°, or by 50% hydrogen bromide in acetic acid at room temperature, but only one equivalent of benzyl bromide could be isolated, the second apparently forming a quaternary salt with the arsine.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 9th*, 1946.]

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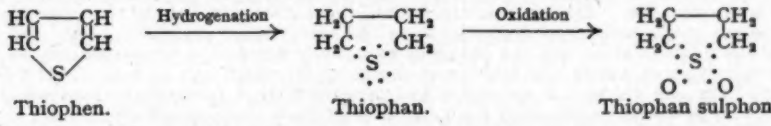
115. *Studies in the Detoxication of Catalyst Poisons. Part V. Thiophen.*

By E. B. MAXTED.

The detoxication of thiophen by the general method used for other poisons in previous papers of this series has been studied (i) for thiophen added as a poison to a hydrogenation system containing crotonic acid as the unsaturated substance, (ii) for thiophen added to pure benzene, and (iii) for technical benzene containing thiophen as a natural impurity. Complete detoxication can be reached in each case; but the detoxication of systems having a relatively high thiophen content requires repeated detoxication treatment.

THE detoxication of thiophen is of importance in connection with the catalytic hydrogenation of technical benzene, in which it occurs as a poison. As with carbon disulphide (see Part IV, *J.*, 1946, 23), the conversion of thiophen into a shielded derivative, by oxidation, involves the application of a preliminary hydrogenation step during which the thiophen, by virtue of its preferential adsorption on the metallic catalyst used, undergoes preferential hydrogenation

to thiophan which, although still toxic, differs from thiophen in its ease of oxidation to a sulphone. The course of the detoxication is therefore :

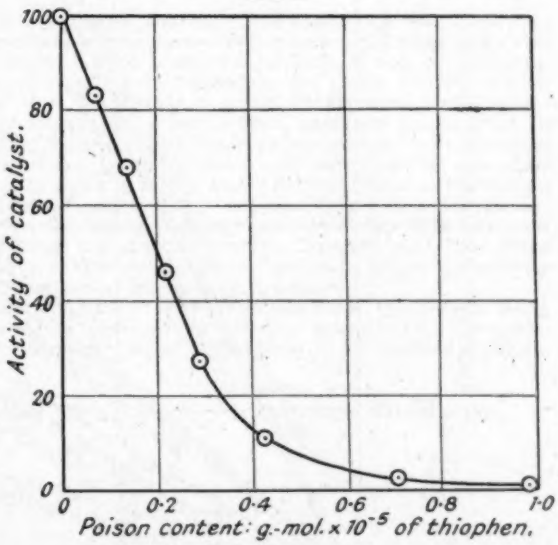


Thiophen. Thiophan. Thiophan sulphone.

the electronic configuration of the potentially toxic sulphur atom in thiophan and in the sulphone being indicated in the usual way. It will be seen that the sulphone possesses a shielded structure and is therefore non-toxic and no longer obstructively adsorbed on the catalyst, the surface of which then becomes free for the ordinary hydrogenation of the unsaturated substance in which the thiophen occurs as an impurity.

The principal difficulty in detoxication by a single hydrogenation–oxidation treatment lies in the effective limitation of the hydrogenation stage to the thiophen originally adsorbed on the catalyst. Amounts of thiophen of this order can be quickly and completely hydrogenated; and the subsequent oxidation stage leads easily to complete detoxication. If larger amounts of thiophen are present, the hydrogenation of any thiophen remaining in the free phase appears to proceed very slowly on account of the slowness of the exchange of thiophen and thiophan between the free and the adsorbed phases, since all poisons have long adsorbed lives. Concentrations of thiophen higher than that originally adsorbable by the catalyst present can, however, be completely detoxicated by repeating the alternate hydrogenation and oxidation. The second stage, involving the quantitative oxidation of thiophan to the sulphone, presents no difficulty.

FIG. 1.



EXPERIMENTAL.

The general technique was similar to that described in previous papers of this series (*J.*, 1945, 204, 764, 766; 1946, 23). For the establishment of suitable conditions, the thiophen was, in earlier experiments, added as a poison to a hydrogenation system containing crotonic acid as a convenient unsaturated substance, since this can readily be obtained free from sulphur. Following this work, thiophen was added in known quantities to sulphur-free benzene; and, finally, the detoxication of technical benzene, in which thiophen occurs naturally, was studied. The hydrogenation catalyst used throughout was platinum black. The detoxicating reagent employed for the oxidation phase was permolybdic or perphosphoric acid, in each case in the presence of an excess of hydrogen peroxide. It has previously been shown that these reagents do not appreciably attack the double bonds of the unsaturated substances in which the thiophen is present as a poison.

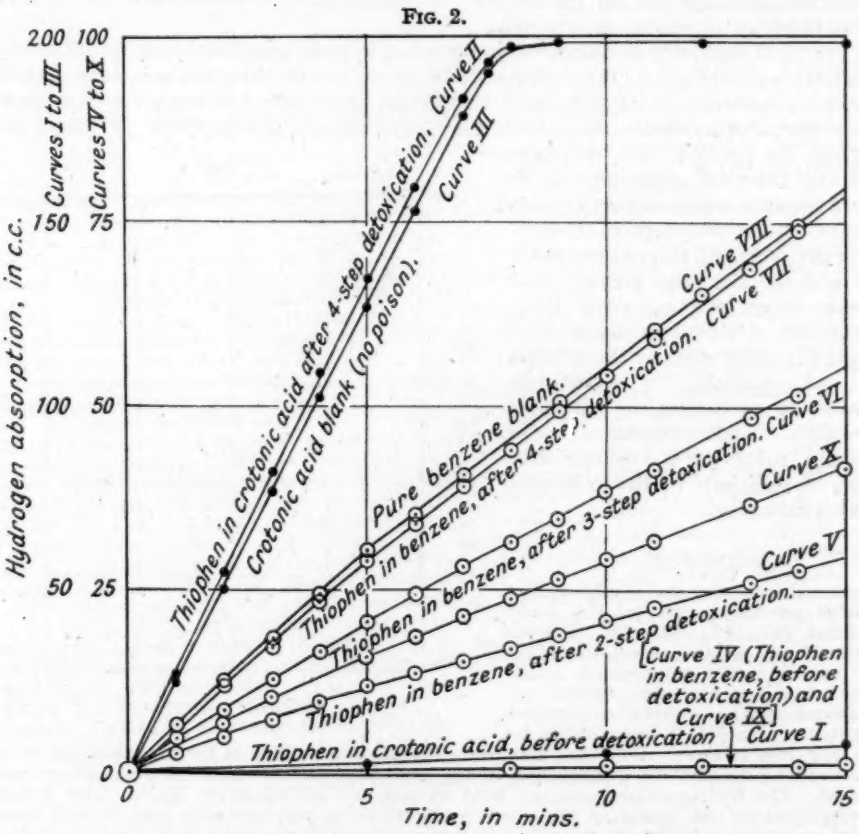
Thiophen in Crotonic Acid.—The standard system taken for treatment consisted of 0·075 g. of stock platinum black, suspended in 5 c.c. of a 2N-solution of crotonic acid in acetic acid and poisoned by 10^{-5} g.-mol. of thiophen (in a further c.c. of acetic acid), the system being subsequently made up to 12 c.c. by adding 6 c.c. of water including that added with the detoxicating reagent and water used for rinsing. This amount of thiophen was sufficient to poison the catalyst down to about 2% of its original activity. The poisoning curve, on which the adoption of 10^{-5} g.-mol. of thiophen as a standard poisoning charge was based, is shown in Fig. 1. It will be seen from the form of this curve that the destruction of poison, by detoxication, will only begin to have a large effect on the hydrogenation velocity after 60—70% of the original poison has been destroyed, *i.e.*, after the original 10^{-5} g.-mol. of thiophen has been reduced to an amount below $3 - 4 \times 10^{-6}$ g.-mol.

It was found that, although complete destruction of this amount of thiophen could not be reached by a single preliminary hydrogenation followed by the addition of a detoxicant, as in the work on carbon disulphide described in Part IV, complete detoxication could nevertheless be obtained by repeating the alternate hydrogenation and oxidation. This is illustrated by the set of curves marked I, II, and III in Fig. 2. Curve I shows the rate of hydrogenation, at 27°, of the standard charge containing 10^{-5} g.-mol. of thiophen in its original state. Curve II refers to the same system after a detoxication treatment consisting of four short hydrogenations (usually of about 2 minutes each) in a shaker,

followed, after the first hydrogenation, by the addition of 6×10^{-5} g.-mol. of permolybdic acid and, after each of the subsequent hydrogenations, of 0·075 g. (about 2×10^{-3} g.-mol.) of hydrogen peroxide, the excess of per-acid or peroxide being destroyed by heating, as previously described, before the subsequent hydrogenation. During this treatment, the activity of the catalyst can be observed to rise progressively with each short hydrogenation followed by an oxidation; but, under these conditions, complete detoxication was not obtained by a lesser number of hydrogenation–oxidation steps. Further, the progressive rise in the activity of the catalyst, which can be seen directly by the rate of absorption of hydrogen during the successive hydrogenation steps, is especially rapid at later stages of the detoxication, as would be expected from the form of the toxicity graph (Fig. 1). This rise through intermediate detoxication values was studied in greater detail for thiophen in benzene. Curve III is a blank run, without the addition of poison.

Detoxication of Thiophen in Benzene.—Stocks of thiophen-free benzene were prepared in two ways. In the first of these, *cyclo*hexane—which, from its method of preparation by the catalytic hydrogenation

FIG. 2.



of benzene with nickel, should already be free from sulphur—was dehydrogenated over palladium at 300° (Zelinski, *Ber.*, 1911, **44**, 3121), a low pressure being used in order to push the equilibrium as far as possible towards benzene. In the second method of preparation, technical benzene, which still contained 0·09% of sulphur (as thiophen), was subjected to the exhaustive adsorption of poisons by finely divided platinum in the absence of hydrogen until no further improvement in the hydrogenation velocity of samples taken for testing occurred on further treatment. Each of these stocks was hydrogenated at about the same velocity, corresponding with the absorption of hydrogen at a steady rate of 5·2—5·3 c.c. per minute under the standard conditions used in the present series; but, since the first stock still contained, on the basis of its refractive index, a little *cyclo*hexane, and since the purity of the second stock (in the sense of its freedom from sulphur) had been confirmed by the equality of its hydrogenation rate to that of the benzene made from *cyclo*hexane, this second stock was used for the detoxication measurements.

In this series, the standard system consisted in each case of 1 c.c. of benzene, dissolved in 10 c.c. of acetic acid, 0·1 g. of stock platinum catalyst, and 2 c.c. of water including that added with the detoxicating reagent. The hydrogenation runs for testing the activity of the catalyst were carried out at 50°; but preliminary hydrogenation for the conversion of thiophen into thiophan, which appears to take place very quickly as far as the adsorbed thiophen is concerned and in any case preferentially to the hydrogenation of benzene, was carried out at room temperature in order, especially at later stages in the detoxication, not to use up too much of the benzene. However, in the preliminary or intermediate

hydrogenations, which form a part of the detoxication process and which were usually carried out for three minutes each, the volume of hydrogen adsorbed was less than 3 c.c. in early stages of the detoxication and did not exceed 10 c.c. in later stages, the hydrogen value of the benzene present being a little less than 800 c.c.

The set of curves marked IV—VIII in Fig. 2 indicates the progress of the detoxication (*i.e.*, the gradual recovery by the platinum of its unpoisoned activity) obtained by repeating the detoxication treatment, each step consisting of a preliminary hydrogenation followed by the addition of a detoxicating regeant which, in this series, was perphosphoric acid. Curve IV shows the very low hydrogenation rate in the presence of 10^{-5} g.-mol. of thiophen without detoxication, and Curve VIII the unpoisoned hydrogenation rate in a blank experiment with pure benzene in the absence of thiophen.

The intermediate curves, V, VI, and VII, show the gradually increasing detoxicating effect obtained respectively by two, three, and four successive additions of detoxicant, preceded in each case by a short (2—3 mins.) hydrogenation. The detoxicant added consisted, in the first step, of $1{\cdot}25 \times 10^{-4}$ g.-mol. of perphosphoric acid and, for subsequent steps, of 2×10^{-3} g.-mol. (0·075 g.) of hydrogen peroxide. It will be seen from Curve VII that substantially complete detoxication was reached after four combined steps, each consisting of a short hydrogenation followed by an oxidation.

The lack of response of thiophen to detoxication by oxidation only, without prior hydrogenation, is shown in Curve IX, in which the charge, containing 10^{-5} g.-mol. of thiophen, was subjected to a 4-step addition of the above quantities of the oxidising reagent as in Curve VII but without preliminary or intermediate hydrogenation. The points in Curve IX fall almost exactly on those of Curve IV. Even if only a single preliminary hydrogenation was applied, followed by a 4-step oxidation, as in earlier work with carbon disulphide, the resulting detoxication was relatively poor (see Curve X, which should be compared with Curve VII).

Detoxication of Technical Benzene.—The benzene taken was the stock containing 0·09% of total sulphur, almost all of which was present in the form of thiophen. This percentage corresponds with $2{\cdot}8 \times 10^{-3}$ g.-mol. of thiophen per c.c. Accordingly, if 1 c.c. is taken in making up each experimental charge, as in the runs with pure benzene with artificially added thiophen, the poison content will be about three times that in the previous series. For this reason, it would be expected that a larger number of combined detoxication steps will be required in order to reach complete detoxication, in view of the apparent limitation of the preliminary hydrogenation phase to thiophen actually adsorbed on the catalyst. In addition to runs with 1 c.c. of the impure benzene, tests were therefore also made with charges containing smaller amounts. Save for this and for the use of permolybdic acid (in amount corresponding to $0{\cdot}6 \times 10^{-4}$ g.-atom of Mo) in the first oxidation step, in place of the $1{\cdot}25 \times 10^{-4}$ g.-mol. of perphosphoric acid used in the previous series, the standard charge and conditions of detoxication were identical with those already described in detail for artificial benzene–thiophen mixtures. Even the smallest volume (0·25 c.c.) of this impure benzene contained sufficient poison to reduce the activity of the catalyst to a negligibly low value in the absence of detoxication treatment.

Some of the results with technical benzene are summarised in the following table. As before, 100% detoxication denotes the complete recovery by the catalyst of its unpoisoned activity, *i.e.*, the attainment, in the main hydrogenation test, of a reaction velocity equal to that given in the absence of poison.

C.c. of benzene in charge.	G.-mol. of thiophen present $\times 10^5$.	Number of detoxication steps.	Detoxication, %.	Number of detoxication steps.	Detoxication, %.
0·25	0·7	(0	3)	2	94
		1	59	3	100
0·5	1·4	(0	2)	5	100
		4	89		
1·0	2·8	(0	<2)	7	75
		5	10	8	100
		6	34		

It will be seen that about 8 treatments were required for the complete detoxication of a charge containing 1 c.c. of the impure benzene, the number being reduced to about 5 treatments for 0·5 c.c. and to about 3 for 0·25 c.c. This necessity for repeated treatment if the benzene contains a relatively large quantity of thiophen is the principal practical disadvantage in the application of the present general method to benzene. The objection does not hold for the other poisons studied in previous papers; *e.g.*, carbon disulphide (Part IV), which resembles benzene in requiring preliminary hydrogenation, could be successfully detoxicated after one preliminary hydrogenation only; and cystein (Parts II and III) responds easily to per-acid detoxication even without any preliminary hydrogenation. The possibility of introducing modifications in the detoxication procedure in order to avoid this necessity for repeated treatment in the case of thiophen is being considered separately.

It may also be mentioned that preliminary work on the detoxication of technical naphthalene has shown that the poisons (principally thionaphthen) contained in this substance can readily be detoxicated in an adsorbed state: thus, a platinum catalyst which had previously been poisoned with commercial naphthalene was found to recover its original activity after hydrogenation followed by treatment with perphosphoric acid.

The author wishes to thank the Department of Scientific and Industrial Research for a grant.

UNIVERSITY OF BRISTOL. [*Received, August 26th*, 1946.]

116. *The Kinetics of Halogen Addition to Unsaturated Compounds. Part X. Styrene, Stilbene, and their Derivatives.*

By I. Ting and P. W. Robertson.

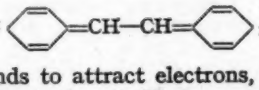
The factors determining the relative rates of addition of bromine to styrene, dimethylstyrene, and stilbene are discussed. Addition to stilbene in acetic acid is decelerated by hydrogen bromide and catalysed only to a small extent by lithium chloride. β-Nitrostyrene adds halogen by the electrophilic mechanism 10^6 times more slowly than styrene, and its rate of bromine addition in acetic acid is accelerated by sulphuric acid and very considerably by hydrogen bromide. It thus resembles cinnamaldehyde, and a similar nucleophilic mechanism is possible for the two compounds. Dinitrostilbene shows both a low electrophilic and a low nucleophilic rate of halogen addition.

Bromine addition to styrene has been measured by the competition method (Ingold and Ingold, *J.*, 1931, 2354), and the relative rates established, $CHPh{:}CH_2$ 3 > $CHMe{:}CH_2$. The superiority of Ph to Me as an electron donor in electrophilic halogen addition was confirmed by direct kinetic measurement of the rates of chlorine addition to the compounds, $CHPh{:}CH{\cdot}CO_2H$ 9 > $CHMe{:}CH{\cdot}CO_2H$ (Part V, *J.*, 1945, 129). Bauer and Moser (*Ber.*, 1907, **40**, 918) found that stilbene added bromine slowly in carbon tetrachloride and more rapidly in chloroform, without, however, making a detailed kinetic study of the reactions. In methylalcoholic solution, addition of bromine becomes more rapid, the products being *s.*-dibromodibenzyl and α-bromo-β-methoxydibenzyl, and Meinel (*Annalen*, 1934, **510**, 219; 1935, **516**, 237) concluded that the brominating agent was MeOBr. A comprehensive investigation of this reaction by Bartlett and Tarbell (*J. Amer. Chem. Soc.*, 1936, **58**, 466) revealed that the results were in accord with a mechanism of electrophilic attack by the bromine molecule.

Styrene adds bromine in acetic acid solution at a rate too rapid for detailed kinetic measurement. Substitution of a β-hydrogen atom in this compound by Ph causes a large rate reduction, as is indicated by the following relative rates (values for $CMe_2{:}CHPh$ and $CMe_2{:}CHMe$ added for comparison):

$CMe_2{:}CHMe$	$CMe_2{:}CHPh$	$CHPh{:}CH_2$	$CHPh{:}CHPh$
>10	1·3	1	0·012

As two methyl groups joined to the same carbon atom are superior to a phenyl group in electron-donating power, the electrophilic attack is chiefly on the α-carbon atom (*A*). The

(*A*.) $Me_2C{=}CHPh$ $\quad\quad$ $\mp$  $\pm$ (*B*.)

phenyl group now acts in the reverse sense and tends to attract electrons, causing the rate for $CMe_2{:}CHPh$ to be inferior to that of $CMe_2{:}CHMe$ (although Ph is superior to Me as an electron-donor). The rate for stilbene should be less than for $CMe_2{:}CHPh$ but not to so considerable an extent, as judged by reference to related compounds

($CMe_2{:}CH{\cdot}CO_2H$ 10 > $CHPh{:}CH{\cdot}CO_2H$).

It is possible that resonance stabilisation (*B*) as well as a steric effect may operate to reduce the rate of halogen addition to stilbene.

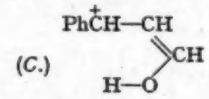
Bromine addition to stilbene in acetic acid solution shows mixed third- and second-order kinetics in the concentration region M/80—M/160 at 24°, as is found for other compounds in this solvent. Rate measurements have also been made with added hydrogen bromide and lithium chloride:

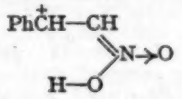
k_2, M/80, = 18 $\quad$ + M/20-HBr, k_2 = 7·8 $\quad$ + M/20-LiCl, k_2 = 28

The ratios of catalysed to uncatalysed addition thus obtained, *viz.*, for HBr 0·43, for LiCl 1·6, correspond with the values at the same concentrations for such compounds as allyl benzoate, HBr 0·67, LiCl 1·9 (Part VI). These reactions are considered to proceed by an electrophilic mechanism, and differ from the reactions of compounds which constitutionally tend to favour a nucleophilic mechanism and show considerable catalysis, *e.g.*, $CH_2{:}CHBr$, HBr 10·5, LiCl 7·0 (following communication).

The introduction of the strongly electron-attracting nitro-group in the β-position in styrene causes a very large reduction in the electrophilic rate of halogen addition ($CHPh{:}CH_2$ 10^6 > $CHPh{:}CH{\cdot}NO_2$), and nitrostyrene has its expected position in the series, $CHPh{:}CH{\cdot}CO_2H$ > $CHPh{:}CH{\cdot}CHO$ > $CHPh{:}CH{\cdot}NO_2$ (Part VIII, *J.*, 1945, 888). The nitro-group, moreover,

resembles the aldehyde group in being structurally favourable for hydrogen-ion addition (see *C* and *D*), and consequently acid-catalysed nucleophilic halogen addition is possible. Nitro-


(*C.*)


(*D.*)

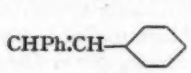
styrene is catalysed by sulphuric acid and hydrogen bromide; herewith are the rates for nitro styrene plus bromine, each M/40 ($x = 20$), in acetic acid at 24° :

+ M/40-NaOAc, $k_2 = 0{\cdot}0019$ + M/40-H_2SO_4, $k_2 = 0{\cdot}0090$ + M/40-HBr, $k_2 = 0{\cdot}83$

The superiority of hydrogen bromide to sulphuric acid as a catalyst, as in the corresponding reactions with cinnamaldehyde, is in accordance with the theory of 1 : 4-addition of HBr_2. With 2 : 4-dinitrostilbene, to which reference is made later, such addition cannot take place, and correspondingly there is no such large difference in effect between the two catalysts for bromine addition.

The nitro-group, which is more strongly electron-attracting than the aldehyde group and consequently has a greater decelerating influence on electrophilic halogen addition, is found to be inferior to it in promoting nucleophilic addition, as is evident from the relative velocities ($CHPh{:}CH{\cdot}CHO$ $3 \times 10^4 > CHPh{:}CH{\cdot}NO_2$) for sulphuric acid catalysed bromine addition in acetic acid solution. A rate-determining change in this mode of addition is the initial reaction, $A + H^+ \rightleftarrows A^+H$ By reference to the formulations (*C*) and (*D*), it is apparent that in (*D*) the $N \rightarrow O$ group by electron attraction tends to cause the splitting off of H^+, and hence to make the rate of acid-catalysed nucleophilic addition to the nitro-compound less than to the aldehyde.

The introduction of nitro-groups into stilbene causes a large reduction in the electrophilic rate of halogen addition, as is apparent from the relative velocities :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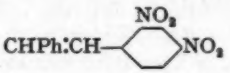
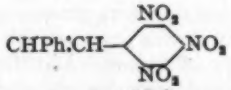

1×10^{-3}


4×10^{-6}

The dinitrophenyl group attached to the ethylene system has a smaller electron-attracting power than the nitro-group; this is shown by the electrophilic rates of chlorine addition in acetic acid at 24° :

$CHPh{:}CH{\cdot}C_6H_3(NO_2)_2$ $k_2 = 12{\cdot}8$ $CHPh{:}CH{\cdot}NO_2$ $k_2 = 0{\cdot}020$

Correspondingly, dinitrostilbene reacts less rapidly than nitrostyrene by the nucleophilic mechanism; herewith are the rates of bromine addition to dinitrostilbene, both M/160, in presence of catalysts in acetic acid at 24° :

$k_2 = 0{\cdot}014$ + M/160-H_2SO_4, $k_2 = 0{\cdot}017$ + M/160-HBr, $k_2 = 0{\cdot}033$

It is evident that the tendency to the tautomeric change involving the nitro-group becomes weakened in being relayed through the benzene nucleus. The relatively small difference in catalytic activity betwen sulphuric acid and hydrogen bromide is ascribed to the impossibility of 1 : 4-addition of HBr_2 to dinitrostilbene.

Experimental.

The following compounds were used in this investigation : styrene, freshly distilled, b. p. 146°/760 mm.; ββ-dimethylstyrene, b. p. 184°/760; β-nitrostyrene, m. p. 57°; stilbene, m. p. 124°; 2 : 4-dinitrostilbene, m. p. 143°; 2 : 4 : 6-trinitrostilbene, m. p. 155°.

The method of experimentation was as previously described and is illustrated for one reaction.

Stilbene, M/80 + Br_2, M/80 in HOAc, 24°; reaction mixture, 10 ml.; 1-ml. samples pipetted into KI and titrated with N/80-$Na_2S_2O_3$:

Time (mins.)	0	0·6	1·7	2·9	4·3	5·5	7·3
Titre (ml.)	1·95	1·73	1·33	1·12	1·00	0·90	0·78

From curve, $x = 50$, $t = 4{\cdot}40$. Second expt., $x = 50$, $t = 4{\cdot}30$. The reaction is typically termolecular.

Br_2 addition, x, %	10	20	30	40	50
$k_3 \times 10^{-3}$	8·5	8·0	8·0	8·3	8·7

Other measurements are given as times (mins.) for $x = 20$ or $x = 50\%$ halogen absorption, reactions in HOAc in the dark, 24°. Stilbene, M/80 + Br_2, M/80 + 4[HBr], $x = 50$, $t = 10{\cdot}0$; + 3·2[LiCl], $x = 50$, $t = 2{\cdot}1$; M/160 + Br_2, M/160, $x = 50$, $t = 13{\cdot}6$. Dinitrostilbene, M/160 + Cl_2, M/160, $x = 50$, $t = 12{\cdot}5$; + Br_2, M/160, $x = 20$, $t = 2800$; + [H_2SO_4], $x = 20$, $t = 2400$; + [HBr], $x = 20$, $t = 1200$. Trinitrostilbene, M/160 + Cl_2, M/160 (solvent HOAc + H_2O, 5%), $x = 50$, $t = 570$. Styrene, M/320 + Br_2, M/320, $x = 50$, $t = 0{\cdot}028$; $\beta\beta$-dimethylstyrene, M/320 + Br_2, M/320, $x = 50$, $t = 0{\cdot}021$ (these two results from a group of observations at $x = \sim 50\%$). β-Nitrostyrene, M/40 + Cl_2, M/40, $x = 20$, $t = 480$; M/40 + Br_2, M/40, $x = 20$, $t = 5100$; + [H_2SO_4], $x = 20$, $t = 1060$; + [HBr], $x = 20$, $t = 12$.

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117. *The Kinetics of Halogen Addition to Unsaturated Compounds. Part XI. The Halogeno-ethylenes.*

By B. E. SWEDLUND and P. W. ROBERTSON.

Whereas bromine addition to vinyl bromide in acetic acid solution is catalysed by both hydrogen bromide and lithium chloride, CHPh:CHBr and CMe_2:CHCl behave differently, bromine addition being decelerated by hydrogen bromide and accelerated by lithium chloride to a relatively small extent. This is further evidence that electrophilic addition of HBr_3 may take place to compounds in which there is considerable electron-accession to the ethylenic system. The rates of chlorine addition to *cis*- and *trans*-1 : 2-dichloroethylene and to trichloroethylene have been measured in aqueous acetic acid solution. The velocity of bromine addition to *s*.-dichloro*iso*butylene is low owing to steric hindrance, and with this compound there is very marked catalysis by hydrogen bromide and lithium chloride. The theoretical significance of these various results is discussed.

REFERENCE was first made to the hydrogen bromide catalysis of bromine addition to vinyl bromide in acetic acid solution in Part I of this series (Robertson *et al.*, *J.*, 1937, 335), and was later confirmed by Nozaki and Ogg (*J. Amer. Chem. Soc.*, 1942, **64**, 697), who also showed that the reaction was greatly accelerated by lithium chloride. These authors considered that such catalysis was characteristic of bromine addition generally, and accordingly formulated a special theory of bromine addition. It has since been demonstrated by us that these effects are not obtained with certain allyl derivatives (Swedlund and Robertson, *J.*, 1944, 131). A similar result is now found for vinyl compounds containing electron-contributing groups, as is evident from the following ratios for catalysed to uncatalysed reactions, reactants M/80, in acetic acid solution :

	CH_2:CHBr ($k_3 = 0{\cdot}42$).	CHPh:CHBr ($k_3 = 52$).	CMe_2:CHCl ($k_3 = 220$).
LiCl (3·2 mols.)	7·0	1·5	2·2
HBr (8 mols.)	10·5	0·49	0·64

Included in the table are the termolecular rates of bromine addition. These are higher than the velocities for the corresponding acids, CHPh:$CH{\cdot}CO_2H$, $k_3 = 5{\cdot}0$, and CMe_2:$CH{\cdot}CO_2H$, $k_3 = 47$, indicating that the carboxyl group is more efficient in reducing the electrophilic rate of halogen addition than chlorine or bromine.

As was found for the allyl halides (Part VI), when there is a small lithium chloride acceleration, hydrogen bromide has a decelerating influence on the rate of bromine addition. Whereas the acceleration caused by lithium chloride increases with its concentration, the effect due to hydrogen bromide becomes constant with excess of catalyst, indicating that HBr_3 is the reactive compound. A nucleophilic mechanism is considered to operate for HBr_3 addition to vinyl bromide, and an electrophilic mechanism for the other two compounds, where there is considerable electron-accession to the ethylene system. Hydrogen bromide causes a change from third- to second-order kinetics, so if hydrogen bromide has a decelerating influence on the rate of bromine addition, this effect becomes relatively greater when the initial concentration of the reactants increases. This is illustrated by the rates of bromine addition to CMe_2:CHCl, quoted below as bimolecular coefficients, in acetic acid at 24° :

	M/40.		M/80.
k_2 ($x = 50$)	0·98	($n = 3{\cdot}1$)	0·46
+8[HBr], k_2 ($x = 50$)	0·30	($n = 2{\cdot}0$)	0·29

The present investigation has been extended to include rate measurements with chloroethylenes containing more than one atom of chlorine. The rate of chlorine addition to *cis*- and *trans*-dichloroethylene under the influence of light has been measured by Chavanne (*Bull. Soc. chim. Belg.*, 1914, **28**, 234). It was found that the relative rates were *trans* > *cis*,

but such measurements with pure compounds are not strictly comparable, as a change in solvent is in effect involved. Chlorine addition to *cis*- and *trans*-dichloroethylene in acetic acid in the dark was inconveniently slow, but measurable rates were obtained in the mixed solvent, HOAc 80% + H_2O 20%, at 24°:

x	10	20	30	40	50
k_2 (*cis*)	0·016	0·014	0·012	0·011	0·011
k_2 (*trans*)	0·0053	0·0054	0·0054	0·0053	0·0051

The normal relative order, *cis* > *trans*, as for other compounds of the general type CH*a*:CH*b*, is now found for these stereoisomers, the ratio for the initial rates being 3 : 1. The *trans*-compound gives constant bimolecular coefficients, but for *cis*-dichloroethylene there is a fall in rate as the reaction proceeds; this is attributed to a partial conversion into the more slowly reacting *trans*-isomer during the course of the reaction. Jones and Taylor (*J. Amer. Chem. Soc.*, 1940, **62**, 3480) have shown that bromine in the dark can cause a partial change from *trans*- to *cis*-dichloroethylene.

Trichloroethylene adds chlorine more slowly than the dichloroethylenes, and its rate was measured in acetic acid containing 40% of water; tetrachloroethylene was found not to react in the dark in this solvent at a measurable rate. The following table shows the relative rates of halogen addition to certain halogen derivatives of ethylene. The ratio measured for the first and second compounds is for iodine addition, for the second and third bromine addition, and for the third, fourth, and fifth compounds chlorine addition.

CH_2:CH_2.	CH_2:CH·CH_2Br.	CH_2:$CHBr$.	CHCl:CHCl (*cis*).	$CHCl$:CCl_2.
1	3×10^{-1}	3×10^{-4}	1×10^{-7}	3×10^{-10}

The decelerating influence of halogen atoms on the rate of addition to ethylenic compounds is thus illustrated. In tri- and tetra-chloroethylene a steric effect, in addition to the electron-attracting power of the chlorine atoms, is probably an additional cause of the low reactivity.

Another type of ethylenic compound which shows steric hindrance to halogen addition is *s*-dichloro*iso*butylene, as is evident from the relative rates:

CH_2:CH_2.	CH_2:CH·CH_2Cl.	CH_2:$C(CH_2Cl)_2$.
1	0·45	0·0055

In the CH_2Cl group the electron-attracting and electron-repelling power tend to neutralise each other, so that one such group attached to an ethylene carbon atom should not be expected to have a large influence on the electrophilic rate. Actually, there is a small reduction in rate, and this effect should be expected to be greater in *s*.-dichloro*iso*butylene, but not to the very large extent experimentally found. According to the theory proposed by Roberts and Kimball (*J. Amer. Chem. Soc.*, 1937, **59**, 947) the two-phase process of halogen addition is completed by the approach of a negative halogen ion to the positive carbon atom, which approach in this compound is hindered by the screen of CH_2Cl groups. An additional effect is possible in this type of compound, namely, a repulsion of the approaching halogen ion by the outer electrons of the chlorine atoms in the CH_2Cl groups, thus tending still further to reduce the rate.

A single CH_2Cl in 3-chloropropylene by its electron-attracting power produces the condition favourable for the nucleophilic mechanism, *i.e.*, hydrogen bromide or lithium chloride catalysis. With *s*.-dichloro*iso*butylene there is similarly catalysis by both, as illustrated by the ratios of the rates of catalysed reactions, M/80-reagents in acetic acid, to the uncatalysed reactions in acetic acid at 24°: 8[HBr], 5·8 : 1, 6·4[LiCl], 35 : 1.

Experimental.

The following compounds were used in this investigation: vinyl bromide, b. p. 16°/760 mm.; *cis*-dichloroethylene, b. p. 59—60°/750 mm.; *trans*-dichloroethylene, b. p. 48—49°/750 mm. (these two compounds from commercial dichloroethylene); trichloroethylene, b. p. 85·7—85·8°/756 mm.; 1-chloro*iso*butylene, b. p. 67·3—67·9°/754 mm.; ω-bromostyrene, b. p. 110—112°/25 mm. The *s*.-dichloro*iso*butylene, CH_2:$C(CH_2Cl)_2$ (*J. Amer. Chem. Soc.*, 1945, **67**, 942), was kindly provided by Professor J. B. Cloke, Troy, N.Y.

The reaction velocities were measured in duplicate or triplicate, as previously described, with specially ground and tested stoppered bottles well shielded from light. In the chlorine experiments the established technique for volatility corrections was used. The measurements with di- and tri-chloroethylene were made in an atmosphere of nitrogen. Herewith is a typical rate determination:

CH_2:$CHBr$, M/10 + Br_2, M/80 in HOAc, 24°; reaction mixture, 10 ml., 1-ml. samples titrated with KI and N/160-$Na_2S_2O_3$:

Time (mins.)	0	660	1590	2850;	0	1210	1980	2660
Titre (ml.)	3·99	3·72	3·42	2·87;	3·99	3·53	3·26	2·98

From combined curve, $x = 10$, $t = 1050$; $x = 20$, $t = 2160$.

Other results are expressed as times (mins.) for x% halogen absorption at 24° in acetic acid, unless otherwise stated. $CH_2{:}CHBr$, M/10 + Br_2, M/80 + M/20-HBr, $x = 20$, $t = 205$; $x = 50$, $t = 690$; + M/10-HBr, results identical; + 0·04M-LiCl, $x = 20$, $t = 310$; $x = 50$, $t = 980$; + 0·08M-LiCl, $x = 20$, $t = 130$, $x = 50$, $t = 490$; $CH_2{:}CHBr$, M/10 + Cl_2, M/80; $x = 20$, $t = 8·0$, $x = 50$, $t = 24$; same reactants in HOAc + 20% H_2O, $x = 50$, $t = 0·32$.

CHCl:CHCl (*cis*) (in nitrogen), M/10 + Cl_2, M/80, in HOAc + 20% H_2O, $x = 20$, $t = 165$, $x = 50$, $t = 700$; same reactants in HOAc + 40% H_2O, $x = 30$, $t = 7·9$. CHCl:CHCl(*trans*) (in nitrogen), M/10 + Cl_2, M/80, in HOAc + 20% H_2O, $x = 20$, $t = 420$, $x = 50$, $t = 1400$.

$CHCl{:}CCl_2$ (in nitrogen), M/10 + Cl_2, M/80, in HOAc + 40% H_2O, $x = 30$, $t = 2700$.

$CMe_2{:}CHCl$, M/80 + Br_2, M/80, $x = 20$, $t = 38·5$, $x = 50$, $t = 175$; + M/10-HBr, $x = 50$, $t = 275$; + 0·08M-LiCl, $x = 50$, $t = 78$.

CHPh:CHBr, M/10 + Br_2, M/80, $x = 20$, $t = 17·7$, $x = 50$, $t = 63$; + M/10-HBr, $x = 50$, $t = 127$; + 0·08M-LiCl, $x = 50$, $t = 30$.

$CH_2{:}C(CH_2Cl)_2$, M/80 + Br_2; M/80, $x = 20$, $t = 1080$, $x = 50$, $t = 3350$; + M/10-HBr, $x = 20$, $t = 115$; $x = 50$, $t = 580$; + 0·08M-LiCl, $x = 20$, $t = 14$, $x = 50$, $t = 95$. Ratio of rates ($x = 10$), A, M/5 + Br_2, M/5: A, M/10 + Br_2, M/5 = 1·95: n(A) = 1·0.

Correction.—The results quoted in *J.*, 1945, 131, for 0·05M- and 0·1M-LiCl should read 0·04M- and 0·08M-LiCl respectively.

Discussion.

Electrophilic halogen addition to vinyl bromide proceeds by an attack on the β-carbon atom, and the low reaction rate, more than 1000 times slower than for ethylene, is due to the simultaneous operation of the inductive effect of the bromine atom in this bromide. Correspondingly in bromobenzene the bromine atom determines the point of attack (*o*, *p*-positions) and at the same time makes the compound less reactive than benzene. To explain the marked lithium chloride catalysis of bromine addition to vinyl bromide, the following mechanism is suggested:

$$CH_2{:}CHBr + Cl^- \rightleftharpoons \bar{C}H_2{-}\underset{Cl}{\overset{Br}{CH}} \xrightarrow{Br_2} CH_2Br{\cdot}CHClBr + Br^-$$

The initial attack by the halide ion may be regarded as similar to that taking place in the Finkelstein reaction. The negative ion thus produced, even if present to a very small extent, would react rapidly with bromine (by the electrophilic mechanism) to complete the reaction. Replacement of the β-hydrogen atoms by electron-repelling groups would tend to inhibit the initial attack by chloride ion on the α-carbon atom, and consequently prevent the catalysis. For a similar reason, in the Finkelstein reaction, the relative velocities are $CH_2{:}CHBr > CHMe{:}CHBr$, with sodium iodide in acetone solution (Juvala, *Ber.*, 1930, **63**, 1998).

The lithium chloride catalysis of addition to *s*-dichloro*iso*butylene is considered to operate by the mechanism proposed for 3-chloropropylene (Part VI, *J.*, 1945, 131):

$$CH_2{:}C(CH_2Cl)_2 + Cl^- \underset{2}{\overset{1}{\rightleftharpoons}} \bar{C}(CH_2Cl)_2 \xrightarrow[3]{Br_2} CH_2Cl{\cdot}CBr(CH_2Cl)_2 + Br$$

By the method of stationary concentrations (if $n = 3$, as is experimentally found)

$$-\,d[Br_2]/dt = (k_1/k_2)k_3[A][Br_2][Cl^-]$$

Compared with the corresponding reaction with 3-chloropropylene, the inductive effect of the chlorine atoms would cause k_1 to be greater, and k_3 to be less [at the same time the resonance stability due to the symmetry of the ion $\bar{C}(CH_2Cl)_2$ would tend to decrease k_2 and k_3], so that the relative velocities of the two compounds cannot be predicted. The especially marked catalysis of bromine addition to *s*-dichloro*iso*butylene (35 times the rate for 6·4 mols. of LiCl at M/80) is due to the fact that the rate of the uncatalysed reaction is low on account of steric hindrance.

With the completion of the present investigation it is now possible to make a critical estimate of the theory of bromine addition elaborated by Nozaki and Ogg in a series of papers (*J. Amer. Chem. Soc.*, 1942, **64**, 697, 704, 709). According to this theory, the addition process may be represented by the rate expression

$$-\,d[Br_2]/dt = k_a[A][Br_2]X^- + k_b[A][Br_2] + k_c[A][Br_2]^2$$

where X^- is an added ion, *e.g.*, Cl^- from lithium chloride.

In support of this theory detailed measurements are made with three compounds, maleic acid, vinyl bromide, and allyl chloride, all of which are found to show considerable catalysis in acetic acid solution, more especially with lithium chloride and bromide and hydrogen bromide. There are less complete observations with allyl acetate, and reference is made to lithium bromide

and hydrogen bromide as catalysts when actually they decelerate bromine addition to this compound. Our study of the kinetics of bromine addition permits a classification of the compounds for which catalysis is to be expected : they are such substances as

$CH_2{:}CH{\cdot}CO_2H$ [or $CH(CO_2H){:}CH{\cdot}CO_2H$], $CH_2{:}CHBr$, $CH_2{:}CH{\cdot}CH_2Cl$ [or $CH_2{:}C(CH_2Cl)_2$],

in which there is an electron-attracting group, or groups, attached to the ethylenic system, the type of compound especially investigated by Nozaki and Ogg, and by implication regarded as typical. In such compounds the electrophilic rate of bromine addition tends to be low, so any catalytic effect depending on the reverse mechanism is liable to become apparent.

As lithium bromide reduces the bromine concentration by formation of the tribromide, and the last is considered to be inactive, lithium chloride should be superior to the bromide as a catalyst, as is found for $CH_2{:}CHBr$ and $CH_2{:}CH{\cdot}CH_2Cl$ (Nozaki and Ogg, *loc. cit.*, pp. 702, 705, 706). A similar result is to be expected for maleic acid, but here measurements only with lithium bromide are recorded. Our experiments reveal that bromine addition to maleic acid in acetic acid is more rapid with added lithium bromide than with the chloride. We find that the latter may even reduce the rate of bromine addition to this type of compound : thus in the reaction, $CHPh{:}CH{\cdot}COPh + Br_2$ in acetic acid at 24°, reactants M/80, $k_2 = 10{\cdot}0$; + LiCl, M/20, $k_2 = 3{\cdot}1$. The explanation is that lithium chloride acts as a base in acetic acid, and therefore reduces the rate of acid-catalysed nucleophilic addition.

Hydrogen tribromide (and its lithium salt, which forms it by acetolysis with acetic acid) is not an inactive reagent as is claimed by Nozaki and Ogg, but may react rapidly with such compounds as αβ-unsaturated acids, aldehydes, ketones and nitro-compounds, by a 1 : 4-addition mechanism. In these reactions the HBr_2 acts as a nucleophilic reagent, since the point of attack is a positive carbon atom. But it appears that HBr_2 may also react by an electrophilic mechanism, *e.g.*, with compounds like allyl benzoate (Part VI) and stilbene (Part X), for which the nucleophilic mode of addition is not to be expected. Therefore, in the reaction between allyl acetate and bromine, the small effect of hydrogen (and lithium) bromide is not because the contribution of the bromine addition reaction is relatively considerable (Nozaki and Ogg, *loc. cit.*, p. 712), but because the bromine addition reaction is eliminated and replaced by an HBr_2 addition reaction, the rate of which, at the concentrations measured, is not considerably different. Such a difference increases, however, as the concentrations become greater, since the orders of the two reactions are not the same, as demonstrated for $CMe_2{:}CHCl$ in the present communication.

With reference to the second (bimolecular) term in their rate expression, Nozaki and Ogg consider (p. 715) that this involves a simultaneous attack on the unsaturated molecule by bromine and the solvent, which donates acetate ions. This, it is claimed, is in accordance with the experimental finding that the proportion of liberated hydrogen bromide in the reaction between allyl acetate and bromine becomes greater in more dilute solutions (Nozaki and Ogg, *loc. cit.*, p. 712). If, therefore, the reaction rate is dependent on the contribution of acetate ions, sodium acetate, which is considerably dissociated in acetic acid solution, should exert a considerable influence on the rate of bromine addition. Our experiments show that this is not so : for instance, with stilbene, the relative rate ratio of bromine addition at M/80, at 24°, with 4 and 1 molecules of added sodium acetate, is only 1·1 : 1, and with benzoylstilbene, under the same conditions, a still smaller ratio was found. We therefore conclude that the bimolecular rate is determined by the attack of bromine on the unsaturated molecule, and that the production of hydrogen bromide is due to a secondary process which is not rate-determining. Bromine addition in acetic acid is thus similar to its addition in a polar aprotic solvent such as chlorobenzene, in which similar kinetics are observed (Part VII).

Nozaki and Ogg do not discuss the nature of the high-order reaction (the third term in the rate expression) nor do they make any reference to our previous investigation of the allyl acetate–bromine reaction in the concentration range M/40—M/3000 (*J.*, 1939, 1515). Concentrations of ~ M/20 represent the upper experimental limit for rate measurements with this type of compound, but certain halogenoethylenes have now been investigated at higher concentrations in acetic acid at 24°, with the following results, $x = 50$, times (mins.) :

	M/5.		M/10.		M/20.		M/40.
$CHPh{:}CHBr$	1·5	($n = 3{\cdot}6$)	9·1	($n = 3{\cdot}2$)	4·3	($n = 2{\cdot}9$)	165
$CH_2{:}C(CH_2Cl)_2$	8·5	($n = 3{\cdot}5$)	47	($n = 3{\cdot}2$)	220		*

* n(M/20—M/80) = 2·9.

It seems that a reaction of a higher order than third gradually takes control at the upper concentration. A fourth-order reaction could be explained by the participation of associated

bromine molecules, which, in the polar form $Br^+–Br_3^-$, would be reactive. Whilst there is no evidence for the existence of associated bromine molecules in acetic acid solution, a very small concentration might be sufficient to give the effect observed. A quadrimolecular reaction at a measurable rate is inconceivable if it involves a simultaneous collision between four molecules, but it is not impossible if it is regarded as a three-stage process, in each of the stages of which one at least of the reactants is in excess.

$$Br_2 + Br_2 \rightleftarrows Br_4;\ Br_4 + A \rightleftarrows A,Br_2 + Br_2;\ A,Br_2 + Br_2 \rightarrow ABrBr + Br_2$$

Alternatively, the first two stages might be regarded as a three-molecule process, $A + 2Br_2$. However, if such a fourth-order reaction does take place, it might be argued that bromine addition in the concentration region M/40, where there is third-order kinetics, is due to the equal contribution of the second- and the fourth-order reactions. If this were so, there would be a much more rapid falling off in order than observed with decrease in concentration; it can be calculated that the fourth-order reaction would become virtually eliminated at M/160 (when its contribution becomes 1/16 of that of the bimolecular reaction). But experiment shows that it requires as low a concentration as M/2000 to establish the bimolecular rate. We therefore express the velocity of bromine addition by

$$-d[Br_2]/dt = k_2[A][Br_2] + k_3[A][Br_2]^2 + k_4[A][Br_2]^3$$

the middle term being dominant in the concentration region M/20—M/80.

The similarity between addition and substitution by bromine has previously been stressed (*J.*, 1943, 279), and a similar mechanism proposed for the two modes of reaction. Experiments (by P. B. D. de la Mare) now reveal that the order higher than third, found for the bromination of certain hydrocarbons in acetic acid solution, is shown by other compounds also. An account of this work will be given in a future communication.

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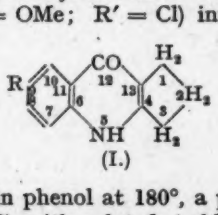
118. *Some Amino-derivatives of Dihydro-β-quinindene and Tetrahydroacridine.*

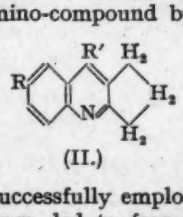
By V. PETROW.

Amino-derivatives of dihydro-β-quinindene and tetrahydroacridine have been prepared. Nitration of 5-chlorotetrahydroacridine gives 5-chloro-9-nitrotetrahydroacridine, together with some of the 6-nitro-isomeride, identified after reduction and hydrolysis as *6-amino-1 : 2 : 3 : 4-tetrahydroacridone*.

THE object of the present study, carried out during 1942—1944, was the preparation of some amino-derivatives of dihydro-β-quinindene (II) and tetrahydroacridine (III) for biological examination. Both these compounds occupy structurally an intermediate position between the quinolines and the acridines, two classes of compound which have been extensively studied from the chemotherapeutic standpoint. Biological results obtained on some of the following compounds, however, were not sufficiently encouraging to warrant a further extension of the work.

The dihydro-β-quinindenes (II; R′ = NH_2) were prepared essentially employing the method of Blount, Perkin, and Plant (*J.*, 1929, 1982). Ethyl *cyclo*pentanonecarboxylate was condensed with the appropriate anilines at room temperature, and the water-free anilino-derivatives added to boiling liquid paraffin. The resulting *12-keto-2 : 3 : 5 : 12-tetrahydro-β-quinindenes* (I) were converted into the *12-chloro-2 : 3-dihydro-β-quinindenes* (II; R′ = Cl) by heating with phosphorus oxychloride. Attempts to convert *12-chloro-9-methoxy-2 : 3-dihydro-β-quinindene* (II; R = OMe; R′ = Cl) into the 9-amino-compound by passage of ammonia through its


(I.)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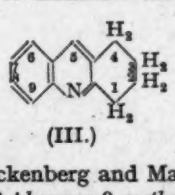
(III.)

solution in phenol at 180°, a procedure successfully employed by Backenberg and Marais (*J.*, 1942, 382) with related 4-chloroquinaldines, led to formation of *12-phenoxy-9-methoxy-2 : 3-*

dihydro-β-quinindene (II; R = OMe; R′ = OPh) in high yield. The desired *amino*-compounds (II; R′ = NH_2) were ultimately prepared in 50—60% yields by heating the chloro-compounds (II; R′ = Cl) in sealed tubes with saturated alcoholic ammonia at 220—240°, in the presence of a trace of a copper salt. In common with related 4-aminoquinaldines, acetylation of *12-amino-2 : 3-dihydro-β-quinindene* (II; R = H; R′ = NH_2) gave a *diacetyl* derivative. The *monoacetyl* derivative was obtained by reaction of the base with a small excess of acetic anhydride in pyridine solution.

5-Aminotetrahydroacridine was prepared by the action of alcoholic ammonia (copper salt as catalyst) on 5-chlorotetrahydroacridine (Braun, Heymons, and Mans, *Ber.*, 1931, **64**, 227) at 220—240°. It was not obtained when ammonia was passed through a solution of the chloro-compound in phenol at 180°, the product being *5-phenoxytetrahydroacridine*. Albert and Gledhill (*J. Soc. Chem. Ind.*, 1945, **64**, 169T) have since prepared 5-aminotetrahydroacridine by this method, employing *p*-cresol as a solvent. Acetylation of 5-aminotetrahydroacridine gave a bright yellow *diacetyl* derivative. The ultra-violet absorption curve of this compound was practically identical with that of the colourless 12-diacetylaminodihydro-β-quinindene (above), so it does not seem necessary to postulate a 5-iminoacridan type of structure for this compound to account for its yellow colour (cf. Wilkinson and Finar, *J.*, 1946, 115). The *monoacetyl* derivative was prepared by the same means as that recorded in the preceding paragraph.

Reduction of 5-chloro-7-nitro-1 : 2 : 3 : 4-tetrahydroacridine (Magidson and Travin, *J. Gen. Chem. Russ.*, 1937, **7**, 819) with reduced iron in acidulated aqueous alcohol gave *5-chloro-7-amino-1 : 2 : 3 : 4-tetrahydroacridine*, characterised by preparation of an *acetyl* derivative. Reaction with alcoholic ammonia in a sealed tube yielded the 5 : 7-*diamino*-compound, which gave only a *diacetyl* derivative on acetylation. *5-Chloro-8-amino-1 : 2 : 3 : 4-tetrahydroacridine* was similarly prepared from the corresponding nitro-compound (Magidson and Travin, *loc. cit.*), and characterised as the *acetyl* derivative. Conversion of 9-nitrotetrahydroacridone (Perkin and Sedgwick, *J.*, 1924, 2442) into the corresponding *5-chloro-9-nitro-1 : 2 : 3 : 4-tetrahydroacridine* was unsatisfactory owing to considerable resinification. The latter compound was more conveniently prepared by direct nitration of 5-chlorotetrahydroacridine. Reduction gave *5-chloro-9-amino-1 : 2 : 3 : 4-tetrahydroacridine*, characterised by an *acetyl* derivative, and converted by alcoholic ammonia at 240° into the 5 : 9-*diamino*-compound. Reduction of the more soluble fractions from the nitration of 5-chlorotetrahydroacridine apparently gave a new homogeneous *5-chloro-aminotetrahydroacridine*. This compound is probably a molecular addition complex of the 6- and 9-amino-5-chlorotetrahydroacridines. On acetylation followed by fractionation from glacial acetic acid, it gave *ca.* 30% of 5-chloro-9-acetamidotetrahydroacridine, hydrolysed by hydrochloric acid to the amino-compound. Crystallisation of the more soluble fractions from aqueous alcohol gave a product of indefinite m. p. (*ca.* 176°) admixed with some much higher-melting material. This observation suggested hydrolysis to the tetrahydroacridone during crystallisation from the aqueous alcohol. The more soluble fractions were therefore digested with 10% acetic acid for 8 hours, and finally submitted to fractionation, whereby *6-acetamido-1 : 2 : 3 : 4-tetrahydroacridone* was obtained in 25% yield, smoothly hydrolysed by hydrochloric acid to the *amino*-derivative. The formulations assigned to the last two compounds rested on their non-identity with the known 7-, 8-, and 9-aminotetrahydroacridone analogues, previously described by Perkin and Sedgwick (*ibid.*, pp. 2444, 2445).

Experimental.

(M. p.'s are corrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.)

12-Amino-2 : 3-dihydro-β-quinindene (II; R = H; R′ = NH_2).—9-Chlorodihydro-β-quinindene (5 g., Blount and Plant, *J.*, 1937, 377), saturated alcoholic ammonia (20 ml.), and a trace of copper acetate were heated in a sealed tube at 220—240° for 20 hours. The alcohol was removed, and the residue extracted several times (charcoal) with boiling water. The bulked filtrates were made alkaline with excess of 30% sodium hydroxide solution, and the precipitated solids crystallised from aqueous acetone. *12-Amino-2 : 3-dihydro-β-quinindene* formed silky needles, m. p. 183—183·5° (Found: C, 78·1; H, 6·5; N, 15·2. $C_{13}H_{13}N_3$ requires C, 78·3; H, 6·5; N, 15·2%). The *hydrochloride* formed octahedra from alcohol, m. p. >310° (Found: Cl, 16·1. $C_{13}H_{13}N_3$,HCl requires Cl, 16·1%). The *diacetyl* derivative, angular plates from aqueous methyl alcohol, m. p. 172—173° (Found: C, 72·0; H, 6·0; N, 11·2. $C_{16}H_{16}O_2N_3$ requires C, 71·6; H, 6·0; N, 10·5%), was obtained when the base (4 g.) was heated under reflux with acetic anhydride (30 ml.) and a little anhydrous sodium acetate for 30 minutes. *12-Acetamido-2 : 3-dihydro-β-quinindene*, octahedra from aqueous methyl alcohol, m. p. 229·5—230·5° (decomp.) (Found: C, 74·3; H, 6·1; N, 12·3. $C_{14}H_{14}ON_3$ requires C, 74·3; H, 6·2; N, 12·4%), was obtained when the amino-compound (4 g.), acetic anhydride (4 ml.), and dry pyridine (8 ml.) were heated under reflux for 30 minutes, and the cooled product treated with excess of dilute ammonium hydroxide.

12-Keto-9-methoxy-2 : 3 : 5 : 12-tetrahydro-β-quinindene (I; R = OMe).—Ethyl *cyclo*pentanone-carboxylate (20 g.) and powdered *p*-anisidine (15 g.) were stirred at room temperature until solution was

complete. After a further 7 days the crystalline product was washed with a little ice-cold methyl alcohol, powdered, dried in a vacuum desiccator, and added to liquid paraffin at 280°. The mixture was vigorously stirred and kept at this temperature until reaction was complete with no further separation of crystalline material. After standing overnight, the solids were collected, thoroughly washed with hot benzene until free from liquid paraffin, and recrystallised from spirit (charcoal). *12-Keto-9-methoxy-2 : 3 : 5 : 12-tetrahydro-β-quinindene* formed glistening white needles, m. p. >310° (Found: C, 72·2; H, 6·0; N, 6·5. $C_{13}H_{13}O_2N$ requires C, 72·6; H, 6·1; N, 6·5%).

12-Chloro-9-methoxy-2 : 3-dihydro-β-quinindene (II; R = OMe; R′ = Cl).—The foregoing compound (1 g.) was heated under reflux with phosphorus oxychloride (10 ml.) for 1½ hours. Excess of phosphorus halides was removed under reduced pressure on the water-bath, and the residue decomposed with ice–dilute ammonium hydroxide. The precipitated solids were collected and crystallised from aqueous methyl alcohol. *12-Chloro-9-methoxy-2 : 3-dihydro-β-quinindene* formed glancing needles, m. p. 125—126° (Found: Cl, 15·3. $C_{13}H_{12}ONCl$ requires Cl, 15·2%); yield nearly quantitative.

12-Phenoxy-9-methoxy-2 : 3-dihydro-β-quinindene (II; R = OMe; R′ = OPh).—The foregoing chloro-compound (1 g.) in phenol at 180—190° was treated with a current of dry ammonia for 2 hours. The product was treated with excess of dilute sodium hydroxide solution, and the solids collected and crystallised from light petroleum. The *9-methoxy*-compound formed large plates (1·4 g.), m. p. 133—134° (Found: C, 78·4; H, 5·8; N, 5·2. $C_{19}H_{17}O_2N$ requires C, 78·4; H, 5·8; N, 4·8%).

12-Amino-9-methoxy-2 : 3-dihydro-β-quinindene (II; R = OMe; R′ = NH_2) formed squat needles from aqueous acetone, m. p. 217·5° (with blackening) (Found: C, 72·8; H, 6·5; N, 13·5. $C_{13}H_{14}ON_2$ requires C, 72·9; H, 6·5; N, 13·1%). The *hydrochloride* formed needles from aqueous-alcoholic hydrogen chloride, m. p. 308—309° (decomp.) (Found: Cl, 13·1. $C_{13}H_{14}ON_2,HCl,H_2O$ requires Cl, 13·2%).

9-Chloro-12-keto-2 : 3 : 5 : 12-tetrahydro-β-quinindene (I; R = Cl) was prepared from *p*-chloroaniline and formed sparingly soluble silky needles, from glacial acetic acid, m. p. >310° (Found: C, 65·6; H, 4·6; N, 6·4. $C_{13}H_{10}ONCl$ requires C, 65·6; H, 4·6; N, 6·4%). *9 : 12-Dichloro-2 : 3-dihydro-β-quinindene* (II; R = R′ = Cl) formed squat rods from light petroleum, m. p. 115—116° (Found: Cl, 28·8. $C_{13}H_9NCl_2$ requires Cl, 28·8%). The *9-chloro-12-amino*-analogue formed silky needles from aqueous acetone, m. p. 235·5—236° (with blackening) (Found: C, 65·9; H, 5·2; N, 12·9. $C_{13}H_{11}N_2Cl$ requires C, 65·9; H, 5·0; N, 12·8%); its *hydrochloride* formed silky needles from hydrochloric acid, m. p. 316° (decomp.) (Found: Cl, 27·8. $C_{13}H_{11}N_2Cl,HCl$ requires Cl, 27·9%).

9-Dimethylamino-12-keto-2 : 3 : 5 : 12-tetrahydro-β-quinindene (I; R = NMe_2) formed very sparingly soluble, pale yellow microcrystals, m. p. >310° (Found: N, 12·4. $C_{14}H_{16}ON_2$ requires N, 12·3%), showing an intense blue fluorescence in alcohol. *12-Chloro-9-dimethylamino-2 : 3-dihydro-β-quinindene* (II; R = NMe_2; R′ = Cl) formed straw-coloured, silky needles from aqueous alcohol, m. p. 139·5—140·5° (Found: Cl, 14·5. $C_{14}H_{15}N_2Cl$ requires Cl, 14·4%). The *12-amino*-derivative (II; R = NMe_2; R′ = NH_2) formed iridescent octahedra from aqueous alcohol, m. p. 256—257° (Found: C, 73·5; H, 7·3; N, 18·6. $C_{14}H_{17}N_3$ requires C, 74·0; H, 7·5; N, 18·5%); its *trihydrochloride* formed silky needles from hydrochloric acid, m. p. 296·5—297·5° (decomp.) (Found: Cl, 29·9. $C_{14}H_{17}N_3,3HCl,H_2O$ requires Cl, 30·1%).

5-Aminotetrahydroacridine Derivatives.—5-Aminotetrahydroacridine formed octahedra from very dilute alcohol, m. p. 183—184° (Found: C, 78·9; H, 7·0; N, 14·1. Calc. for $C_{13}H_{14}N_2$: C, 78·8; H, 7·1; N, 14·1%). The *hydrochloride* separated from concentrated hydrochloric acid in needles, m. p. 283—284° (efferv. at 110°) (Found: Cl, 14·5. $C_{13}H_{14}N_2,HCl,H_2O$ requires Cl, 14·4%). The *diacetyl* derivative, bright yellow octahedra from aqueous alcohol, m. p. 172·5—173·5° (Found: C, 72·4; H, 6·4; N, 10·3. $C_{17}H_{16}O_2N_2$ requires C, 72·4; H, 6·4; N, 9·9%), was obtained when the amino-compound (4 g.) was heated with acetic anhydride (30 ml.) for 30 minutes under reflux. *5-Acetamidotetrahydroacridine*, white needles from aqueous methyl alcohol, m. p. 249—250° (decomp.) (Found: C, 74·9; H, 6·8; N, 11·7. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7; N, 11·7%), was obtained when the amino-compound (7·5 g.), dry pyridine (15 ml.), and acetic anhydride (7·5 g.) were heated under reflux for 30 minutes. The product was precipitated with dilute ammonium hydroxide, and the precipitated solids crystallised twice; yield, 5·5 g. The mother-liquors deposited the yellow diacetyl derivative on standing.

5-Phenoxytetrahydrodroacridine, irregular plates from light petroleum, m. p. 116—117° (Found: C, 83·1; H, 6·1; N, 5·5. $C_{19}H_{17}ON$ requires C, 82·9; H, 6·2; N, 5·1%), was obtained when 5-chlorotetrahydroacridine (5 g.) in phenol (15 g.) was treated with a current of ammonia at 170—180° for 45 minutes. The phenoxy-derivative was also obtained in somewhat better yield when the chloro-compound (10 g.) was heated with potassium hydroxide (2·8 g.) in phenol (20 g.) at 170° for 30 minutes.

5-Chloro-7-amino-1 : 2 : 3 : 4-tetrahydroacridine.—Powdered 5-chloro-7-nitrotetrahydroacridine (20 g.) (Magidson and Travin, *loc. cit.*), reduced iron (30 g.), water (28 ml.), spirit (72 ml.), and a drop of concentrated hydrochloric acid were heated under reflux for 1 hour. The filtrate and washings were taken to dryness, and the residue crystallised from absolute alcohol (charcoal). The required *compound* (12·7 g.) formed dimorphic straw-coloured octahedra, m. p. 167—168° and 185·5—186·5° (Found: N, 12·1; Cl, 15·2. $C_{13}H_{13}N_2Cl$ requires N, 12·0; Cl, 15·3%), showing an intense blue fluorescence in dilute alcoholic solution. The *monoacetyl* derivative, straw-coloured needles from acetone, m. p. 200—201° (Found: N, 9·8. $C_{15}H_{15}ON_2Cl$ requires N, 10·2%), was obtained when the base (1 g.) was heated with acetic anhydride (5 ml.) for 30 minutes under reflux on the water-bath.

5 : 7-Diamino-1 : 2 : 3 : 4-tetrahydroacridine, pale yellow crystals from aqueous alcohol, m. p. 182·5—183·5° (dried product) (Found: C, 73·2; H, 7·1; N, 19·7. $C_{13}H_{15}N_3$ requires C, 73·2; H, 7·1; N, 19·7%), was obtained when 5-chloro-7-aminotetrahydroacridine (6 g.) was heated with saturated alcoholic ammonia (20 ml.) and a trace of a copper salt at 220—240° for 10 hours. The *diacetyl* derivative, small needles from aqueous alcohol, m. p. >310° (Found: C, 68·6; H, 6·4; N, 14·0. $C_{17}H_{19}O_2N_3$ requires C, 68·7; H, 6·4; N, 14·1%), was obtained when the diamino-compound (1 g.) was heated under reflux with acetic anhydride (10 ml.) until solution was complete (*ca.* 1½ hours).

5-Chloro-8-amino-1 : 2 : 3 : 4-tetrahydroacridine, orange needles from alcohol, m. p. 217—218° (Found: N, 11·9; Cl, 15·3. $C_{13}H_{13}N_2Cl$ requires N, 12·0; Cl, 15·3%), was obtained by reduction of 5-chloro-8-

nitrotetrahydroacridine (Magidson and Travin, *loc. cit.*). The *acetyl* derivative formed angular orange crystals from aqueous methyl alcohol, m. p. 209—210° (Found: N, 10·1. $C_{15}H_{15}ON_3Cl$ requires N, 10·2%).

5-Chloro-9-nitro-1 : 2 : 3 : 4-tetrahydroacridine.—(a) A solution of 5-chlorotetrahydroacridine (60 g.) in concentrated sulphuric acid (200 ml.) was treated at 0° with nitric acid (25 g.; *d* 1·42), added dropwise with mechanical stirring. The product was poured on crushed ice, made alkaline with ammonia, and the precipitated solids crystallised six times from aqueous acetone (charcoal). The required *compound* formed squat pink needles (12 g.), m. p. 139·5—140·5° (Found: N, 10·8; Cl, 13·8. $C_{13}H_{11}O_2N_3Cl$ requires N, 10·7; Cl, 13·6%). (b) 9-Nitrotetrahydroacridone (18 g.) (Perkin and Sedgwick, *loc. cit.*), phosphorus pentachloride (16 g.), and phosphorus oxychloride (50 ml.) were heated under reflux on a water-bath for 30 minutes. The product was poured on crushed ice and decomposed with ammonia. The black tarry product was crystallised from aqueous acetone (charcoal), and gave 5-chloro-9-nitrotetrahydroacridine, m. p. 137—138° (Found: Cl, 13·8%), not depressed in admixture with the compound obtained by method (a); yield, 10%.

5-Chloro-9-amino-1 : 2 : 3 : 4-tetrahydroacridine, faintly coloured plates from aqueous alcohol, m. p. 92—93° (Found: N, 12·2; Cl, 15·7. $C_{13}H_{13}N_2Cl$ requires N, 12·0; Cl, 15·3%), was obtained by reduction of the foregoing nitro-compound. The *acetyl* derivative formed corn-coloured needles from alcohol, m. p. 178·5—179·5° (Found: N, 10·2. $C_{15}H_{15}ON_2Cl$ requires N, 10·2%). *5 : 9-Diamino-1 : 2 : 3 : 4-tetrahydroacridine* formed pale yellow squat needles from alcohol–light petroleum, m. p. 180—181° (Found: C, 73·2; H, 7·1; N, 19·8. $C_{13}H_{15}N_3$ requires C, 73·2; H, 7·1; N, 19·7%).

6-Amino-1 : 2 : 3 : 4-tetrahydroacridone.—The more soluble fractions obtained in the nitration of 5-chlorotetrahydroacridine were freed from resinous material by washing with a little ice-cold acetone, and reduced with reduced iron in acidulated aqueous alcohol. The product was taken up in alcohol, saturated with hydrogen chloride, and the orange hydrochloride collected. The regenerated *base* (? addition complex) formed rhombic crystals from light petroleum, m. p. 114—115° (Found: N, 12·2; Cl, 15·3. $C_{13}H_{13}N_2Cl$ requires N, 12·0; Cl, 15·3%). In admixture with 5-chloro-9-aminotetrahydroacridine a definite depression of 3—4° was obtained. The base (8 g.) was heated under reflux with acetic anhydride (40 ml.) for 30 minutes on the water-bath. The product, isolated in the usual manner, was fractionally crystallised from glacial acetic acid, giving 5-chloro-9-acetamidotetrahydroacridine, m. p. 176°, not depressed in admixture with an authentic specimen, and hydrolysed by concentrated hydrochloric acid during 30 minutes at 100° to 5-chloro-9-aminotetrahydroacridine, m. p. 92—93°, alone or in admixture with an authentic specimen. The more soluble fractions were dissolved in 10% acetic acid and heated under reflux on the water-bath for 8 hours. The base was precipitated with ammonium hydroxide, and gave on crystallisation from aqueous alcohol and finally alcohol–ligroin, pale yellow needles of *6-acetamidotetrahydroacridone*, m. p. 286—287° (Found: C, 70·4; H, 6·2; N, 10·6. $C_{15}H_{16}O_2N_2$ requires C, 70·3; H, 6·2; N, 10·9%), hydrolysed by concentrated hydrochloric acid to *6-amino-1 : 2 : 3 : 4-tetrahydroacridone*, pale yellow platelets from spirit, m. p. >300° (Found: C, 73·0; H, 6·3; N, 13·0. $C_{13}H_{14}ON_2$ requires C, 72·9; H, 6·5; N, 13·1%).

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QUEEN MARY COLLEGE (UNIVERSITY OF LONDON), E.1. [*Received, August 13th*, 1946.]

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119. *Synthesis of Nuclear Amidino-derivatives of 5-Aminoacridine.*

By ALAN A. GOLDBERG and WILLIAM KELLY.

(With a Bacteriological Note by FREDERIC HAYNES.)

5-Amino-2- and -3-amidino-acridines have been synthesised for examination as bacterial inhibitors.

THE high bacteriostatic activity and low tinctorial value of 5-aminoacridine hydrochloride commend its use as a general antiseptic in the place of proflavine. Since the solubility of the compound in physiological saline at ordinary temperatures is lower than is clinically desirable, it was of interest to determine whether the introduction of a nuclear amidino-substituent would improve solubility and possibly enhance antibacterial activity.

In order to obtain amidino-derivatives of 5-aminoacridine it was necessary to prepare cyanodiphenylamine-2-carboxylic acids. The condensation of *o*-chlorobenzoic acid with the three cyanoanilines did not afford the desired intermediates in satisfactory yield; this may be correlated with the observations of Tuttle (*J. Amer. Chem. Soc.*, 1923, **45**, 1916), Bogert, Hirschfelder, and Lauffer (*Coll. Trav. Chim. Czeckoslov.*, 1930, **5**—**6**, 382), and Goldberg and Kelly (*J.*, 1946, 102) upon the inhibiting influence on the Ullmann reaction of negative substituents in the arylamine nucleus. 2-Chloro-5-cyanobenzoic acid and aniline, however, readily condensed to yield *4-cyanodiphenylamine-2-carboxylic acid*, which cyclised with phosphorus oxychloride to *5-chloro-3-cyanoacridine*, and this, on being heated in phenol solution

with ammonium carbonate, yielded *5-amino-3-cyanoacridine*. Conversion of the aminocyanoacridine into the corresponding amino-iminoether at first presented considerable difficulty owing to the almost total insolubility of the dihydrochloride of the former in all anhydrous non-hydroxylic solvents. Success was ultimately attained by reducing the dihydrochlorides to an extremely fine state of subdivision in dioxan by continuous shaking in a closed vessel with glass beads for periods of some 15—20 days. In this manner 5-amino-3-cyanoacridine yielded the amino-iminoether, which was converted by alcoholic ammonia into *5-amino-3-amidinoacridine* in excellent over-all yield. Similarly 5-cyanodiphenylamine-2-carboxylic acid yielded *5-chloro-2-cyanoacridine* which by the same route was converted into *5-amino-2-cyano-* and *5-amino-2-amidino-acridine*. Interaction of 5-amino-2-cyanoacridine with hydroxylamine in boiling aqueous-alcoholic pyridine yielded *5-amino-2-amidoximinoacridine*.

In the same manner 4- and *5-cyano-4'-methoxydiphenylamine-2-carboxylic acids* yielded respectively *5-chloro-2-* and *-3-cyano-7-methoxyacridines* which were converted by the same route into *5-amino-2-* and *-3-amidino-7-methoxyacridines*.

The introduction of the nuclear amidine group into the 2- and 3-positions of 5-aminoacridine effectively increases solubility both in water and in physiological saline but inhibits the *in vitro* bacteriostatic activity against *B. proteus*, *B. pyocyaneus*, *Streptococcus pyogenes*, *Staphylococcus pyogenes aureus*, *B. coli*, *B. typhosus*, and *B. subtilis*.

Experimental.

3'-Cyanodiphenylamine-2-carboxylic Acid.—Potassium *o*-chlorobenzoate (5·0 g.), potassium carbonate (3·0 g.), *m*-cyanoaniline (3·3 g.), and copper powder (0·05 g.) were refluxed in amyl alcohol (15 c.c.) for four hours. The amyl alcohol was removed in steam, the residue filtered with carbon, and the filtrate (150 c.c.) made acid to Congo-red by addition of hydrochloric acid. The gummy precipitate was collected and crystallised twice from alcohol–benzene, *3'-cyanodiphenylamine-2-carboxylic acid* being obtained in yellow prisms (1·0 g.), m. p. 204—205° [Found: N, 11·9; *M* (by titration), 234. $C_{14}H_{10}O_2N_2$ requires N, 11·8%; *M*, 238]. Prolongation of the reaction time failed to increase the yield. Closure of the acridine ring with phosphorus oxychloride gave a mixture, presumably of 5-chloro-2- and -4-cyanoacridines, and accordingly this approach was abandoned. Interaction of *o*-chlorobenzoic acid with *o*- and *p*-cyanoanilines under the same conditions did not yield the required cyanodiphenylamine-carboxylic acids in satisfactory yield.

2-Chloro-4-cyanotoluene.—This was obtained by Magidson and Travin (*Ber.*, 1936, **69**, 537) in 45% yield from 2-chloro-4-aminotoluene by a Sandmeyer reaction with cuprous cyanide; by the use of sodium nickelocyanide, however, the required product could be produced in 87% yield.

2-Chloro-4-aminotoluene (70 g.) was dissolved in water (400 c.c.) and concentrated hydrochloric acid (99 c.c.) and the sludge of hydrochloride diazotised at 0—5° with sodium nitrite (35 g. in 100 c.c. of water). The diazonium solution was added slowly to a boiling solution of sodium nickelocyanide (obtained from 125 g. of sodium cyanide and 125 g. of nickel chloride hexahydrate in 800 c.c. of water), and the mixture refluxed for a further 30 minutes after the addition had been completed. The 2-chloro-4-cyanotoluene was distilled out of the reaction mixture in a current of steam; yield, 65 g. (87%), m. p. 42—44°.

2-Chloro-4-cyanobenzoic Acid.—Oxidation of 80 g. of the foregoing cyano-compound by the method described by Magidson and Travin (*loc. cit.*) afforded 42 g. of 2-chloro-4-cyanobenzoic acid, m. p. 164—168°, which was pure enough for further use, together with 24 g. of recovered chlorocyanotoluene.

5-Cyanodiphenylamine-2-carboxylic Acid.—2-Chloro-4-cyanobenzoic acid (10 g.), potassium carbonate (10 g.), aniline (8 c.c.), amyl alcohol (40 c.c.), and copper powder (0·2 g.) were refluxed together at 150° (bath temp.) for 2½ hours, and the product isolated in the usual manner (Goldberg and Kelly, *loc. cit.*). Recrystallisation from 50% alcohol gave 5-cyanodiphenylamine-2-carboxylic acid (6·5 g.) in yellow-brown plates, m. p. 210—212°. For analysis a sample was recrystallised from aqueous alcohol and obtained in yellow rectangular plates, m. p. 214° [Found: N, 11·7; *M* (by titration), 235. Calc. for $C_{14}H_{10}O_2N_2$: N, 11·8%; *M*, 238].

5-Chloro-2-cyanoacridine.—5-Cyanodiphenylamine-2-carboxylic acid (3·7 g.) was refluxed with phosphorus oxychloride (8·5 c.c.) for 2 hours, the cooled solution quenched on an excess of powdered ice, and the stirred mixture basified with ammonia, the temperature not being allowed to exceed 2°. The precipitate was collected, washed with water, and dried in a vacuum, *5-chloro-2-cyanoacridine* (3·7 g.) being obtained as a green powder, m. p. 192—194°; recrystallisation from benzene (charcoal) gave the pure compound in pale yellow needles, m. p. 197—198° (Found: N, 11·9; Cl, 14·9. $C_{14}H_7N_2Cl$ requires N, 11·7; Cl, 14·9%).

5-Amino-2-cyanoacridine.—The foregoing compound (12·1 g.) was suspended in 5% alcoholic ammonia (300 c.c.) and heated in a closed bottle at 100° for 36 hours. The precipitate was collected from the chilled mixture, and a further amount obtained by evaporation of the filtrate; the total yield was 8·0 g., m. p. 324—326°. Recrystallisation from aqueous pyridine gave *5-amino-2-cyanoacridine* in orange prisms, m. p. 328—329° (Found: C, 76·7; H, 4·1; N, 19·1. $C_{14}H_9N_3$ requires C, 76·7; H, 4·1; N, 19·2%).

5-Amino-2-amidinoacridine.—Anhydrous 5-amino-2-cyanoacridine (4·5 g.) was suspended in anhydrous dioxan (80 c.c.) and anhydrous alcohol (5 c.c.), the mixture saturated with dry hydrogen chloride at 5°, and shaken with glass beads for 26 days in a sealed bottle. The solvent was pumped off at < 40°, saturated anhydrous alcoholic ammonia (130 c.c.) added to the residue, and the whole heated in a closed vessel at 50° for 72 hours. The ammonia and part of the solvent were distilled off at < 40°, the residue chilled, and the crystalline precipitate (3·9 g.) collected; this was found to be a mixture of the

mono- and the di-hydrochloride of the aminoamidinoacridine. The free base was obtained from an aqueous solution of the latter by precipitation with cold dilute sodium hydroxide; recrystallisation from aqueous methyl alcohol gave *5-amino-2-amidinoacridine* in orange-yellow needles, m. p. 305° (Found: C, 70·8; H, 5·2; N, 23·5. $C_{14}H_{12}N_4$ requires C, 71·1; H, 5·1; N, 23·7%). A 1·0% solution of the monohydrochloride in physiological saline (0·9% sodium chloride) has a pH value of 8·4 and remains clear indefinitely at 20°; it has a pale yellow colour and does not appreciably stain tissue. (A 0·1% solution of 5-aminoacridine hydrochloride in physiological saline has pH 6·8 and remains clear for 12—24 hours at 20° and then slowly precipitates long, silky, yellow needles of the aminoacridine hydrochloride which redissolve on warming. The 0·05% solution in physiological saline begins precipitating after 24—48 hours at 20° but the 0·025% solution remains clear indefinitely.)

5-Amino-2-amidoximinoacridine.—5-Amino-2-cyanoacridine (1·4 g.) was dissolved in a mixture of pyridine (15 c.c.), water (3 c.c.), and alcohol (5 c.c.), a solution of hydroxylamine (from 0·89 g. of the hydrochloride and 0·72 g. of anhydrous sodium carbonate in 3·5 c.c. of water) added, and the mixture heated on the water-bath for 1½ hours, then cooled and diluted with water (50 c.c.); the precipitate (1·3 g.) was collected, and recrystallisation from pyridine–alcohol gave hydrated *5-amino-2-amidoximinoacridine* in felted yellow needles, m. p. 254° (decomp.). From methyl alcohol the compound separated in stout yellow prisms, m. p. 264—265° (decomp.), also containing solvent of crystallisation (Found, on material dried at 140°/2 mm.: C, 66·2; H, 4·8; N, 22·5. $C_{14}H_{13}ON_4$ requires C, 66·8; H, 4·8; N, 22·2%). L.D.$_{50}$, 50 mg./kg.; the compound has no curative influence upon mouse trypanosomiasis.

5-Cyano-4′-methoxydiphenylamine-2-carboxylic Acid (compare Magidson and Travin, *loc. cit.*).—2-Chloro-4-cyanobenzoic acid (28·8 g.), *p*-anisidine (20 g.), potassium carbonate (23 g.), copper powder (0·5 g.), and amyl alcohol (60 c.c.) were stirred at 120—125° (bath temp.) for 3½ hours and then at 130—135° for ½ hour. The crude product, isolated in the usual manner, separated as an oil which rapidly hardened; this was collected and extracted with boiling water (3 × 200 c.c.), and the insoluble material recrystallised from 50% aqueous alcohol (220 c.c.), 5-cyano-4′-methoxydiphenylamine-2-carboxylic acid (20 g.) separating in orange-brown plates, m. p. 196°.

5-Chloro-2-cyano-7-methoxyacridine.—This was prepared from 5-cyano-4′-methoxydiphenylamine-2-carboxylic acid by ring closure with phosphorus oxychloride essentially as previously reported by Magidson and Travin. The yield was practically theoretical, the crude vacuum-dried product having m. p. 225—227°.

5-Amino-2-cyano-7-methoxyacridine.—Magidson and Travin (*loc. cit.*) reported the preparation of this material by the action of absolute alcoholic ammonia on the corresponding 5-chloro-compound. Repetition of this method gave the desired *meso*-amine in only small yield, owing presumably to the low solubility of the 5-chloro-compound in the solvent employed. Reaction of the 5-chloro-compound in phenol solution with ammonium carbonate, however, gave much better results. A solution of 5-chloro-2-cyano-7-methoxyacridine (5·0 g.) in molten phenol (25 g.) was heated to 125—130°, ammonium carbonate (3·0 g.) added as fast as the effervescence allowed, and the mixture kept at this temperature for 2 hours. The mixture was cooled, acetone (100 c.c.) added, and the precipitate of hydrochloride collected, washed with acetone, suspended in water and shaken with an excess of cold 2N-sodium hydroxide and glass beads in a closed bottle for 2 hours. The yellow insoluble material (3·3 g.; m. p. 276—278°) was collected, washed, and recrystallised from pyridine–alcohol, 5-amino-2-cyano-7-methoxyacridine being obtained in orange plates, m. p. 282—284° (Found: N, 16·9. Calc. for $C_{15}H_{11}ON_3$: N, 16·9%).

2-Cyano-5-phenoxy-7-methoxyacridine.—5-Chloro-2-cyano-7-methoxyacridine (2·0 g.) was dissolved in phenol (12·0 g.) and heated at 100° for 3 hours. The melt was cooled, ether (50 c.c.) added, and the precipitate collected, suspended in water, and basified with ammonia. Collection of the precipitate and recrystallisation from alcohol gave *2-cyano-5-phenoxy-7-methoxyacridine* (2·0 g.) in fine yellow needles, m. p. 188° (Found: N, 8·8. $C_{21}H_{14}O_2N_2$ requires N, 8·6%).

2-Amidoximino-5-phenoxy-7-methoxyacridine.—The foregoing compound (5·1 g.) was dissolved in 70% alcoholic pyridine (30 c.c.), a solution of hydroxylamine (from 1·65 g. of hydrochloride and 1·35 g. of anhydrous sodium carbonate in 5 c.c. of water) added, and the mixture heated on the water-bath for 1 hour. Methyl alcohol (30 c.c.) was added to the chilled mixture, and the insoluble material collected (3·6 g.) and recrystallised from alcohol containing a little pyridine; *2-amidoximino-5-phenoxy-7-methoxyacridine* separated in felted yellow needles, m. p. 216° (decomp.) (Found: N, 11·9. $C_{21}H_{17}O_3N_3$ requires N, 11·7%).

5-Amino-2-amidino-7-methoxyacridine.—Anhydrous 5-amino-2-cyano-7-methoxyacridine (3·4 g.) was suspended in anhydrous dioxan (50 c.c.) and anhydrous alcohol (3·5 c.c.), and the mixture saturated with dry hydrogen chloride at 5° and then shaken with glass beads in a sealed bottle at room temperature for 17 days; the solvent and hydrogen chloride were pumped off at < 40°, and the residue heated in a closed vessel with anhydrous saturated alcoholic ammonia (120 c.c.) at 50—55° for 96 hours. *5-Amino-2-amidino-7-methoxyacridine monohydrochloride* (2·2 g.) separated on standing on ice in rosettes of yellow needles, m. p. 282—284° (Found: N, 17·8; Cl, 11·7. $C_{15}H_{14}ON_4$,HCl requires N, 18·4; Cl, 11·7%). The free *base*, isolated by basifying a cold aqueous solution of the hydrochloride with cold sodium hydroxide solution, was crystallised from aqueous methyl alcohol and obtained in yellow needles, m. p. 268—270° (Found: C, 67·1; H, 5·5; N, 20·5. $C_{15}H_{14}ON_4$ requires C, 67·6; H, 5·3; N, 21·0%). L.D.$_{50}$, 75 mg./kg.; the compound exerts a slight retarding influence upon the course of *Tr. equiperdum* infections in mice.

5-Amino-2-amidoximino-7-methoxyacridine.—A solution of 5-amino-2-cyano-7-methoxyacridine (3·3 g.) in pyridine (20 c.c.) and alcohol (10 c.c.) was heated on the water-bath, and a solution of hydroxylamine (from 1·85 g. of hydrochloride and 1·60 g. of anhydrous sodium carbonate in 8 c.c. of water) added. The mixture was heated at 100° for 2 hours, water (50 c.c.) added, and the precipitate collected (2·8 g.; m. p. 294°). Recrystallisation from aqueous pyridine gave *5-amino-2-amidoximino-7-methoxyacridine* in yellow plates, m. p. 296° (decomp.) (Found: C, 64·4; H, 5·1; N, 19·5. $C_{15}H_{14}O_2N_4$ requires C, 63·8; H, 5·0; N, 19·8%). L.D.$_{50}$, 50 mg./kg.; the compound has no influence upon trypanosomiasis in mice.

2-Chloro-5-cyanobenzoic Acid.—2-Chloro-5-aminobenzoic acid (60 g.; Goldberg and Kelly, *loc. cit.*), dissolved in water (185 c.c.) and hydrochloric acid (74 c.c.), was diazotised at 0—5° with a solution of sodium nitrite (25 g.) in water (75 c.c.). The diazonium solution was stirred at 0° for 20 minutes, sodium carbonate added until the reaction was no longer acid to Congo-red, and the solution added slowly to a boiling solution of sodium nickelocyanide (from 90 g. of sodium cyanide and 90 g. of nickel chloride hexahydrate in 600 c.c. of water). After the addition, the mixture was boiled for 15 minutes, hydrochloric acid added to acidity to Congo-red, the mixture heated to the boiling point for 20 minutes, cooled, and the brown sludge collected and washed with water. The residue was extracted with hot methyl alcohol (3 × 300 c.c.), the combined extracts concentrated to incipient crystallisation and cooled, and the *2-chloro-5-cyanobenzoic acid* collected (50·5 g.; m. p. 176—177°). Recrystallisation from water gave the compound in colourless silky needles containing water of crystallisation which was lost on drying at 100° to give a white powder, m. p. 178° [Found: N, 8·1; Cl, 19·3; *M* (by titration), 182. $C_8H_4O_2NCl$ requires N, 7·7; Cl, 19·5%; *M*, 181·5].

4-Cyanodiphenylamine-2-carboxylic Acid.—2-Chloro-5-cyanobenzoic acid (18·2 g.), potassium carbonate (15·2 g.), aniline (18·3 g.), amyl alcohol (40 c.c.), and copper powder (0·5 g.) were refluxed together at 150° (bath temp.) for 1½ hours. The excess of aniline and amyl alcohol was removed in steam, and the residual solution filtered (charcoal) and acidified with hydrochloric acid. The precipitate was collected, extracted several times with boiling water, and the insoluble acid crystallised from 50% ethyl alcohol (120 c.c.), *4-cyanodiphenylamine-2-carboxylic acid* being obtained in brown prisms (16·0 g.), m. p. 214—216°. Recrystallisation from aqueous alcohol gave the pure compound in brown leaves, m. p. 220—222° [Found: N, 12·1; *M* (by titration), 238. $C_{14}H_{10}O_2N_2$ requires N, 11·8%; *M*, 238].

5-Chloro-3-cyanoacridine.—4-Cyanodiphenylamine-2-carboxylic acid (15·0 g.) was gently refluxed with phosphorus oxychloride (30 c.c.) for 3 hours, the mixture quenched on an excess of powdered ice, and basified with ammonia, more ice being added in order that the temperature did not exceed 0°. The precipitate was collected, washed with water, and dried in a vacuum (15 g.; m. p. 184—186°). Crystallisation from benzene–petrol gave *5-chloro-3-cyanoacridine* in yellow-brown needles, m. p. 186° (Found: N, 11·6; Cl, 14·6. $C_{14}H_7N_2Cl$ requires N, 11·7; Cl, 14·9%).

5-Amino-3-cyanoacridine.—A solution of 5-chloro-3-cyanoacridine (8·0 g.) in phenol (80 g.) was heated at 100°, and ammonium carbonate (5·0 g.) added slowly, the mixture being heated at 100° (internal) for a further 1 hour; it was then cooled and diluted with dry ether (300 c.c.), and the precipitate collected and washed with ether. This was shaken with dilute sodium hydroxide and glass beads, the insoluble material collected (5·5 g.; m. p. 304—306°), washed with water, and crystallised from aqueous pyridine, *5-amino-3-cyanoacridine* being obtained in fine yellow needles, m. p. 313° (Found: C, 76·3; H, 3·9; N, 19·3. $C_{14}H_9N_3$ requires C, 76·7; H, 4·1; N, 19·2%).

5-Amino-3-amidinoacridine.—5-Amino-3-cyanoacridine (4·7 g.) was suspended in anhydrous dioxan (60 c.c.) and anhydrous ethyl alcohol (6·0 c.c.), the mixture saturated at 5° with dry hydrogen chloride, and the ground with glass beads in a closed bottle for 28 days at room temperature. The solvent was pumped off at 20—30°, and the residue heated at 45—50° for 72 hours in a closed vessel with anhydrous saturated alcoholic ammonia (125 c.c.). The ammonia and excess of alcohol were pumped off at < 40°, leaving a crystalline residue (4·4 g.) of the mono- and di-hydrochloride of the required amino-amidine. In order to obtain the free base, the cold aqueous solution of the foregoing mixture of hydrochlorides was shaken and very dilute sodium hydroxide added slowly with scratching; *5-amino-3-amidinoacridine* separated in yellow plates, m. p. 302—304° (decomp.) (Found: C, 70·6; H, 5·1; N, 24·0. $C_{14}H_{12}N_4$ requires C, 71·1; H, 5·1; N, 23·7%). A 1·0% solution of the monohydrochloride in physiological saline remains clear indefinitely at 20°; this solution has a pale amber colour and does not appreciably stain tissue.

4-Cyano-4′-methoxydiphenylamine-2-carboxylic Acid.—A mixture of 2-chloro-5-cyanobenzoic acid (9·4 g.), *p*-anisidine (6·6 g.), potassium carbonate (7·4 g.), copper powder (0·2 g.), and amyl alcohol (40 c.c.) was stirred at 125—130° (bath temp.) for 3 hours. The crude product was isolated in the usual manner, extracted with boiling water, and the insoluble residue recrystallised from aqueous alcohol, *4-cyano-4′-methoxydiphenylamine-2-carboxylic acid* (9·5 g.) being obtained in yellow plates, m. p. 212—214°. For analysis, a sample was recrystallised from aqueous alcohol and obtained in yellow rectangular plates, m. p. 214° [Found: N, 10·6; *M* (by titration), 265. $C_{15}H_{12}O_3N_2$ requires N, 10·4%; *M*, 268].

5-Chloro-3-cyano-7-methoxyacridine.—The foregoing acid (7·8 g.) was refluxed with phosphorus oxychloride (16 c.c.) for 3 hours, the reaction mixture quenched on ice, and the precipitate of hydrochloride collected and ground with powdered ice and dilute ammonia. The *5-chloro-3-cyano-7-methoxyacridine* (7·5 g.; m. p. 255—260°) was collected and dried in a vacuum; recrystallisation of a sample from xylene (charcoal) gave the compound in yellow plates, m. p. 270—272° (Found: N, 10·0; Cl, 13·3. $C_{15}H_9ON_2Cl$ requires N, 10·4; Cl, 13·2%).

5-Amino-3-cyano-7-methoxyacridine.—A solution of the preceding compound (6·0 g.) in phenol (40 g.) was heated with ammonium carbonate (4·5 g.) at 125—130° for 2 hours. The reaction mixture was cooled, diluted with dry ether (200 c.c.), and the precipitated hydrochloride collected. The free base (4·4 g.) was liberated by grinding with dilute sodium hydroxide and purified by dissolution in warm dilute acetic acid, filtering with carbon, and reprecipitating with dilute sodium hydroxide. Crystallisation from methyl alcohol gave *5-amino-3-cyano-7-methoxyacridine* in stout yellow prisms, which on drying at 100° lost solvent of crystallisation, giving a yellow microcrystalline powder, m. p. 302—304° (Found: C, 72·1; H, 4·6; N, 16·9. $C_{15}H_{11}ON_3$ requires C, 72·3; H, 4·4; N, 16·9%).

5-Amino-3-amidino-7-methoxyacridine.—The foregoing amine (4·4 g.) was suspended in dry dioxan (60 c.c.) and anhydrous ethyl alcohol (6·0 c.c.) and saturated with dry hydrogen chloride at 5°. The mixture was shaken at room temperature for 10 days, the solvent pumped off at 20°, and the residue heated at 40—45° with anhydrous saturated alcoholic ammonia (100 c.c.) for 96 hours. The excess of ammonia and alcohol was distilled away at 20° under reduced pressure, leaving a crystalline mixture of the hydrochlorides of the required aminoamidine and unchanged cyanoamine. The very soluble aminoamidine hydrochloride was dissolved out by lixiviation with cold water, and the filtered solution

rendered faintly alkaline to phenolphthalein with ammonia in order to precipitate the small amount of cyanoamine which it contained. Basification of the agitated filtered solution with very dilute sodium hydroxide and scratching effected precipitation of *5-amino-3-amidino-7-methoxyacridine* in microscopic yellow needles, m. p. 272—274° (Found, in material dried over phosphoric oxide at 2 mm.: C, 67·3; H, 5·4; N, 21·3. $C_{15}H_{14}ON_4$ requires C, 67·6; H, 5·3; N, 21·0%).

Bacteriological Note.—The median lethal dose ($L.D._{50}$) and maximum tolerated dose (M.T.D.) of 5-amino-2-amidinoacridine hydrochloride, 5-amino-3-amidinoacridine hydrochloride and 5-aminoacridine hydrochloride were determined for a single intraperitoneal injection into 6 weeks old white mice.

Compound.	$L.D._{50}$.	M.T.D.
5-Amino-2-amidinoacridine hydrochloride	70 mg./kg.	50 mg./kg.
5-Amino-3-amidinoacridine hydrochloride	50 ,,	40 ,,
5-Aminoacridine hydrochloride	55 ,,	45 ,,

The antibacterial activities were determined in "Lab-Lemco" broth (A) and in "Lab-Lemco" broth containing 10% normal horse serum (B). The maximum bacteriostatic dilutions of the compounds against a range of standard organisms, as indicated by total absence of observable growth after 24 hours' incubation at 37°, were found to be as follows:

	5-Amino-2-amidino-acridine.		5-Amino-3-amidino-acridine.		5-Aminoacridine.	
	A.	B.	A.	B.	A.	B.
Organism.	1 part in		1 part in		1 part in	
B. proteus	<1,000	<1000	<1,000	<1000	64,000	64,000
B. pyocyaneus	4,000	4000	4,000	1000	2,000	2,000
Streptococcus pyogenes, N.T.C. 2400	8,000	4000	8,000	4000	128,000	64,000
Staphylococcus pyogenes aureus ...	8,000	4000	8,000	4000	128,000	64,000
B. coli	16,000	8000	16,000	2000	64,000	64,000
B. typhosus	16,000	4000	16,000	4000	128,000	32,000
B. subtilis	16,000	4000	16,000	8000	128,000	64,000

WARD, BLENKINSOP & CO. LTD.,
RESEARCH LABORATORIES, BRADFORD-ON-AVON, ENGLAND. [*Received, August 19th*, 1946.]

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120. *Some αββ-Triarylacrylonitriles, αββ-Triarylacrylic Acids, and their Derivatives.*

By NG. PH. BUU-HOÏ and JEAN LECOCQ.

A number of diaryl ketones have been condensed in the presence of sodamide with various arylacetonitriles to give *αββ*-triarylacrylonitriles, which could be converted by alkaline hydrolysis into *αββ*-triarylacrylic acids through the corresponding amides. In some instances, both of the required stereoisomeric forms of the dissymetric nitriles could be isolated. Many of the substances described have been found to be rather oestrogenic and are now under test for other physiological properties.

IN the course of a search for oestrogenic compounds which may also act as growth-inhibitors for malignant tumours, as does diethylstilboestrol, our attention has been directed to substances related to triphenylethylene; moreover, it has recently been observed that certain oestrogens of the same type may also interfere with the experimental production of tumours by carcinogenic hydrocarbons (Lacassagne, Buu-Hoï, and Rudali, 1946). For these reasons, triphenylethylene derivatives, and particularly the related nitriles were deemed worthy of a detailed investigation.

The most convenient way to prepare triarylacrylonitriles (I) is the condensation of diaryl ketones with the sodio-derivatives of arylacetonitriles (cf. Bodroux, *Bull. Soc. chim.*, 1911, **9**, 758):

$$CAr'Ar''O + Ar{\cdot}CH_2{\cdot}CN \longrightarrow CAr'Ar'':CAr{\cdot}CN\ (I.) + H_2O$$

Bodroux prepared triphenyl-, αβ-diphenyl-, β-*p*-tolyl-, and αβ-diphenyl-β-(α'-naphthyl)-acrylonitrile (the last in very low yields), but he ignored the possibility that when unsymmetrical diaryl ketones are used, two stereoisomeric nitriles may be produced. We have extended his reaction to a number of diversely substituted diaryl ketones and arylacetonitriles, and thus obtained a series of triarylacrylonitriles, some of which were obtained in the two required stereoisomeric forms. In accordance with Koelsch's observations upon the properties of stereoisomeric triarylacrylic acids (*J. Amer. Chem. Soc.*, 1932, **54**, 2487), we have found that the

trans- are generally far more soluble than the *cis*-compounds, and that the latter easily undergo extensive stereomutation under the influence of heat.

All of these nitriles are highly crystalline substances which, with one exception (see p. 644), give deep violet halochromic colorations with pure sulphuric acid. Mild treatment with alcoholic alkalis results in formation of the corresponding amides, which also dissolve in sulphuric acid with a deep halochromic coloration.

On treating triphenylacrylonitrile with a boiling solution of potassium hydroxide in amyl alcohol, Bodroux (*loc. cit.*) obtained the amide, but failed to effect further hydrolysis. We have found that complete hydrolysis is achieved by long heating with very concentrated alkali. This method of preparing triphenylacrylic acid is far more convenient than either carboxylation of triphenylvinylmagnesium bromide (Koelsch, *J. Amer. Chem. Soc.*, 1932, **54**, 2045) or treatment of a sulphuric solution of the amide with sodium nitrite (Heyl and Meyer, *Ber.*, 1895, **28**, 2785). Using the same procedure, we also obtained from ββ-diphenyl-α-*p*-anisylacrylonitrile (*cis*-form) an acid which was identical with *trans*-ββ-diphenyl-*p*-anisylacrylic acid prepared by another method by Koelsch (*loc. cit.*). The presence of many methoxyl groups does not appear to interfere with the saponification process, for we obtained α-phenyl-ββ-di-*p*-anisylacrylic acid without difficulty by that method. Application of Bouveault's process to the saponification of ββ-*diphenyl*-α-p-*tolylacrylamide* afforded a small yield of the corresponding *acid*.

When fluorenone was added to an ethereal solution of the sodio-derivative of phenylacetonitrile, a violent reaction took place, accompanied by formation of an abundant precipitate; after hydrolysis, however, only fluorenone and phenylacetonitrile could be isolated, these compounds being recovered almost quantitatively. An attempt to condense anthraquinone with phenylacetonitrile failed similarly.

Experimental.

Triphenylacrylic Acid.—A mixture of triphenylacrylonitrile (5 g.), sodium hydroxide (15 g.) and *iso*amyl alcohol (50 g.) containing a few drops of water was heated under reflux for 72 hours and then poured into water; the aqueous layer was separated, freed from traces of amyl alcohol by a short boiling, and acidified with dilute hydrochloric acid. The flocculent precipitate (1·5 g.) was collected by suction, thoroughly washed with water, and crystallised twice from aqueous acetic acid; slender colourless prisms, m. p. 213°, were thus obtained.

αβ-Diphenyl-β-p-tolyacrylamide.—αβ-Diphenyl-β-p-tolyacrylonitrile, m. p. 123° (3·1 g.) (Bodroux, *loc. cit.*), was heated during one hour with a solution of sodium hydroxide (10 g.) in *iso*amyl alcohol (35 g.) containing a few drops of water. On cooling, the mixture yielded colourless crystals of *αβ-diphenyl-β-p-tolyacrylamide* (3 g.); after recrystallisation from 50% aqueous acetic acid, it formed microscopic glinting needles, m. p. 208—210° (Found: N, 4·5. $C_{22}H_{19}ON$ requires N, 4·4%).

ββ-Diphenyl-α-p-tolylacrylonitrile.—A mixture of *p*-tolylacetonitrile (5 g.), dissolved in anhydrous ether (50 c.c.), and freshly prepared sodamide (2 g.) was gently refluxed until evolution of ammonia had ceased, and the brownish-red solution was slowly treated with benzophenone (5 g.) dissolved in ether. A violent reaction set in immediately; after it had subsided, heating was continued for a further hour, the reaction mixture poured into ice-water, the organic layer collected and dried (Na_2SO_4), and the solvent distilled off. The brownish-red oil which remained crystallised partly on standing overnight; the solid was filtered off, and, after recrystallisation from acetic acid, slender colourless prisms (6 g.), m. p. 153°, were obtained (Found: N, 4·4. $C_{22}H_{17}N$ requires N, 4·7%), giving a deep violet colour with sulphuric acid. The *amide* formed almost colourless needles, m. p. 216°, from aqueous acetic acid (Found: N, 4·4. $C_{22}H_{19}ON$ requires N, 4·4%).

A solution of the above amide (1·1 g.) in pure sulphuric acid (15 g.) was slowly treated with sodium nitrite (0·3 g.) under ice-cooling; the resulting mixture was kept at room temperature for 24 hours, and then poured into water. The reddish precipitate was collected, thoroughly washed with water, and extracted with an aqueous solution of sodium carbonate. The alkaline filtrate was acidified with dilute hydrochloric acid, and the precipitate recrystallised from aqueous acetic acid. *ββ-Diphenyl-α-p-tolylacrylic acid* (0·5 g.) was thus obtained as fine, almost colourless needles, m. p. 237—238°, which gave with sulphuric acid an intense green coloration which rapidly became violet and finally red (Found: C, 84·2; H, 5·6. $C_{22}H_{18}O_2$ requires C, 84·0; H, 5·7%).

ββ-Diphenyl-α-m-tolylacrylonitrile.—*m*-Tolylacetonitrile (7 g.), dissolved in ether, was treated with sodamide (2·5 g.) and then with benzophenone (4 g.) exactly as in the foregoing example. After standard treatment, the *nitrile* (5 g.) crystallised from aqueous acetic acid in brilliant, colourless prisms, m. p. 122° (Found: N, 4·6%). The corresponding *amide* formed colourless needles, m. p. 177°, from aqueous acetic acid (Found: N, 4·2%).

β-Phenyl-αβ-di-p-tolylacrylonitrile.—This was similarly formed from *p*-tolylacetonitrile (6·7 g.) in ether, sodamide (2·5 g.), and *p*-methylbenzophenone (8 g.). The thick yellowish oily *nitrile* first obtained, solidified after distillation (b. p. 235°/3·5 mm.), and formed almost colourless prisms, m. p. 114—115°, from acetic acid (Found: N, 4·2%). The corresponding *amide* formed a colourless micro-crystalline powder from aqueous acetic acid, m. p. 237° (Found: N, 4·2%).

αβ-Diphenyl-β-p-chlorophenylacrylonitrile.—The sodio-derivative prepared from phenylacetonitrile (7·6 g.) and sodamide (3 g.) was allowed to react with *p*-chlorobenzophenone (10 g.) in ether. After standard treatment, a *nitrile* (10 g.) was obtained (from acetic acid) as very feebly yellow prisms, m. p. 139—140°, which were rather soluble in ether, and were therefore probably the *trans*-form (Found: N, 4·6. $C_{21}H_{14}NCl$ requires N, 4·4%).

β-Phenyl-β-p-chlorophenyl-α-p-tolylacrylonitrile.—The reaction between the sodio-derivative of *p*-tolylacetonitrile (from 8·5 g. of nitrile and 3 g. of sodamide) and *p*-chlorobenzophenone (10 g.) afforded after standard treatment an extremely viscous oil which slowly solidified after vacuum distillation (10 g.) (b. p. 245°/4 mm.). It crystallised from aqueous acetic acid as a bright yellow microcrystalline powder, m. p. 147—148° (Found: N, 4·1. $C_{22}H_{16}NCl$ requires N, 4·2%). The corresponding *amide* formed tiny, colourless needles, m. p. 197°, from aqueous acetic acid (Found: N, 3·8 $C_{22}H_{18}ONCl$ requires N, 4·0%).

αβ-Diphenyl-β-p-anisylacrylonitriles.—Phenylacetonitrile (6 g.) in ether was treated with sodamide (2·5 g.) and then with *p*-methoxybenzophenone (8·7 g.), heating being prolonged during 2 hours. The reaction mixture was poured into ice-water, and the abundant yellow precipitate thus obtained was collected by filtration and, crystallised twice from acetic acid, cis-*αβ-diphenyl-β-p-anisylacrylonitrile* (9 g.), formed pale yellowish prisms, m. p. 166° (Found: N, 4·3. $C_{23}H_{17}ON$ requires N, 4·5%). The filtrate was evaporated under diminished pressure, and the residue, which solidified on standing with some drops of acetic acid, gave on recrystallisation from the same solvent, trans-*αβ-diphenyl-β-p-anisylacrylonitrile* (1 g.) as almost colourless needles, m. p. 124—125° (Found: N, 4·2%). The ratio *cis* : *trans* obviously depended on the quality of the sample of sodamide used in the condensation, for in another experiment using an old specimen of this reagent, only the *trans*-isomer was obtained. cis-trans-*Conversion*: The *cis*-isomer was heated in a vacuum, and the glassy distillate (b. p. 245°/4 mm.) crystallised from aqueous acetic acid in tiny, almost colourless prisms, the m. p. (126—128°) of which was not depressed by admixture with a sample of the *trans*-nitrile prepared as above.

αβ-Diphenyl-β-p-anisylacrylamides.—(a) cis-*Isomer.* When heated for 3 hours with a solution of sodium hydroxide (7·5 g.) in aqueous amyl alcohol (25 g.), the foregoing *cis*-nitrile (2·5 g.) afforded an *amide*, which crystallised from aqueous acetic acid in yellow prisms, m. p. 196—198° (Found: N, 4·1. $C_{23}H_{19}O_2N$ requires N, 4·2%). (b) trans-*Isomer.* From a sample of the *trans*-nitrile, an *amide* was similarly obtained in yellow needles, m. p. 176—180° (Found: N, 4·2%) deeply depressed upon admixture with the foregoing amide.

ββ-Diphenyl-α-p-anisylacrylonitrile.—Reaction of *p*-methoxyphenylacetonitrile (6 g.) with sodamide (2 g.) was slow, and required freshly distilled samples of nitrile as well as an active sodamide. Heating was prolonged for 3 hours after ammonia had ceased to be evolved, and an ethereal solution of benzophenone (5 g.) was added. After a further hour's refluxing and standard treatment of the deep red mixture, the *nitrile* (5 g.) was obtained from acetic acid as short yellow needles, m. p. 149° (Found: N, 4·2%). The *amide* crystallised from aqueous acetic acid in slender prisms, m. p. 198° (Found: N, 4·4%).

β-Phenyl-αβ-di-p-anisylacrylonitrile (trans-*Form*).—The viscous yellow oil obtained from the sodio-derivative of *p*-methoxyphenylacetonitrile (7·5 g.) and *p*-methoxybenzophenone (7 g.) did not crystallise spontaneously, and was therefore submitted to vacuum-distillation. A glassy resin, b. p. 260°/4·5 mm., was thus obtained, which readily solidified on standing overnight with a few drops of acetic acid. After recrystallisation from the same solvent, slightly yellow needles, m. p. 122—125°, were obtained (7·5 g.), which were very easily soluble in ether as expected of the trans-*form* (Found: N, 4·0. $C_{25}H_{21}O_2N$ requires N, 4·1%). The trans-*amide* crystallised from dilute acetic acid in yellow prisms, m. p. 243° (Found: N, 3·7. $C_{25}H_{23}O_3N$ requires N, 3·9%).

α-Phenyl-ββ-di-p-anisylacrylonitrile.—Phenylacetonitrile (6 g.) in ether (50 c.c.) was treated with sodamide (2·5 g.) and then with a suspension of 4 : 4′-dimethoxybenzophenone (10 g.) in ether. After decomposition with ice-water, the crystals which separated were redissolved in hot acetic acid (charcoal). On cooling, the *nitrile* (10 g.) was obtained in microscopic, faintly yellow needles, m. p. 159° (Found: N, 4·2%).

A mixture of the foregoing nitrile (7 g.), sodium hydroxide (21 g.), and aqueous amyl alcohol (70 g.) was refluxed during 3 hours; the *amide* which separated on cooling was recrystallised from 50% aqueous acetic acid, giving slender needles, m. p. 209° (Found: N, 4·0%). When the heating was prolonged for 3 days, the acid was obtained; it formed yellow needles from acetic acid, m. p. 169°, as given by Koelsch (*loc. cit.*).

α-p-Tolyl-ββ-di-p-anisylacrylonitrile.—*p*-Tolylacetonitrile (6·7 g.) in ether (50 c.c.) was treated with sodamide (2·5 g.) and then with 4 : 4′-dimethoxybenzophenone (10 g.). After an hour's boiling, the reaction mixture was poured into ice-water; a large quantity of unchanged ketone was precipitated, and was filtered off. The filtrate was dried (Na_2SO_4) and afforded, after evaporation of the solvent and crystallisation from 80% aqueous acetic acid, slender needles of the *nitrile* (7 g.), m. p. 110—111° (Found: N, 4·2. $C_{24}H_{21}O_2N$ requires N, 3·9%), giving a deep violet coloration with pure sulphuric acid. The corresponding *amide* formed yellow needles, m. p. 213°, from aqueous acetic acid (Found: N, 3·9. $C_{24}H_{23}O_3N$ requires N, 3·7%).

αβ-Diphenyl-β-3 : 4-dimethoxyphenylacrylonitriles.—Phenylacetonitrile (7·6 g.) was successively treated with sodamide (3 g.) and with a suspension of 3 : 4-dimethoxybenzophenone (11·2 g.) in ether. After addition of water, the solid which separated was collected by suction and recrystallised from acetic acid. The cis-*nitrile* (8 g.) was thus obtained as slender yellow prisms, m. p. 181° (Found: N, 4·0. $C_{25}H_{21}O_2N$ requires N, 4·1%). The ethereal filtrate was dried (Na_2SO_4), the solvent removed, and the solid residue recrystallised from aqueous acetic acid, giving the trans-*nitrile* (2 g.) as almost colourless needles, m. p. 143—145°, readily soluble in ether (Found: N, 4·1%). On alkaline saponification, both isomers gave the same *amide*, crystallising from aqueous acetic acid in slender yellow needles, m. p. 198° (Found: N, 4·1. $C_{23}H_{21}O_3N$ requires N, 3·9%); as it is generally assumed that the *trans*-compounds are the more stable towards heat, it may be inferred that this is the *trans*-amide.

αβ-Diphenyl-β-2 : 4-dimethoxyphenylacrylonitrile.—Phenylacetonitrile (7 g.) in ether was treated successively with sodamide (2·3 g.) and an ethereal suspension of 2 : 4-dimethoxybenzophenone (10 g.). After decomposition of the reaction mixture, a precipitate (6 g.) was obtained. Recrystallisation from 90% acetic acid gave microscopic yellow prisms, m. p. 146—148° (sintering at 142°) (Found: N, 4·2%). This *substance* could be distilled without isomerisation (b. p. 235°/0·4 mm.).

α-Phenyl-ββ′-bis-(p-dimethylaminophenyl)acrylonitrile.—The action of Michler's ketone (15 g.) upon the sodio-derivative of phenylacetonitrile (9·2 g. of nitrile with 3·5 g. of sodium amide) afforded a deep

coloured semi-solid suspension which was treated with ice-water. The yellow precipitate obtained was chiefly composed of recovered ketone, and was removed by filtration. The filtrate was concentrated, and the deposited solid recrystallised from ethanol. The *amino-nitrile* (0·5 g.) thus obtained formed deep yellow silky needles, m. p. 185°, which did not give any coloration with sulphuric acid (Found: N, 11·1. $C_{16}H_{15}N_3$ requires N, 11·4%).

The authors wish to thank Dr. Nguyen-dat-Xuong for the gift of samples of *p*-methoxyphenylacetonitrile and of Michler's ketone, and Professor Baranger for his keen interest in their researches. This work is being continued.

THE LABORATORY OF ORGANIC CHEMISTRY,
ÉCOLE POLYTECHNIQUE, PARIS.

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121. *The Infra-red Spectra of Solid and Liquid Alkylphenols.*

By T. A. KLETZ and W. C. PRICE.

The infra-red spectra of twelve phenols have been obtained in the liquid and in the solid state in the range 5—15 μ. One of the most striking features of the spectra is the formation of doublets on crystallisation. This is interpreted as being due to association involving hydrogen bonds. Another noteworthy feature is a tendency for the bands to move towards shorter wave-lengths. Considerable changes of intensity occur in some of the bands, particularly those associated with the C–O valency vibration. This is attributed to specific types of hydrogen bonding occurring in the crystal. Crystallisation is also accompanied by a decrease in band width which is apparently due to the greater order prevailing in the crystal and the consequent reduction in collision broadening.

RELATIVELY little work has been done on the comparison of the infra-red spectra of organic substances in the crystalline and the liquid state. This field of investigation appears to be a promising one and must be regarded as an important part of a more general spectroscopic attack upon the solid state which is now engaging the attention of many spectroscopists from both the theoretical and the experimental point of view. It is to be expected that from the changes in the spectrum accompanying the change of state, some information might be found concerning (*a*) the nature of the intermolecular forces which hold the individual molecules together in the crystal lattice, (*b*) the particular isomeric configurations which are likely to be associated with different crystalline modifications, (*c*) the extent to which inter- and intra-molecular hydrogen bonding when present are involved in the formation of the lattice, (*d*) the influence of the crystal symmetry on the molecular motions, (*e*) the possibility of elucidating the types of environment occurring in the unit cell, etc. Some work has already been done on the Raman spectra of crystals by the Indian school of physicists, and some general theoretical treatment of selection rules, relative intensities, etc., in crystals is available (Bhagavantam and Venkatarayudu, *Proc. Indian Acad. Sci.*, 1939, **9** *A*, 224; 1941, **13** *A*, 543; Halford, *J. Chem. Physics*, 1946, **14**, 8). It would be desirable to record the spectra of the gas, the liquid, and the solid, but in the present work this was not possible. The object here has been to attempt to classify empirically the effects which occur in a set of related molecules.

The general conclusions which have been derived from *X*-ray work on organic crystals are that they are predominantly molecular structures (in contrast to most inorganic crystals which are largely macromolecules) and that the molecules remain as discrete units in the lattice. The arrangement in the crystal depends upon the stoicheiometric relations and relative sizes of the atoms rather than abrupt changes of chemical bond type. The present work is concerned with alkylphenols which have melting points in the range 25—80°. The examination in the solid and the liquid condition of the spectra of substances melting in this range does not require very elaborate apparatus, and it appeared possible that any results obtained might be correlated in some degree with the structure of the different alkylphenols and might yield some information concerning the factors mentioned in the previous paragraph.

Experimental.—The spectrometer used was a Hilger D. 209. It was fitted with a rock-salt prism and operated on single beam. On account of the extremely strong absorption of the materials being investigated, it was necessary to use cells of only 0·01 mm. thickness. The cell was placed on an electrically heated stage of special construction situated in front of the slit of the spectrometer. It was then filled with the molten phenol and its temperature was kept just above the m. p. of the substance for the recording of the liquid spectrum which was taken over the range 5—15 μ. After the record had been obtained the heating current was switched off and the substance allowed to crystallise. The scatter of the resulting thin crystalline layer was found to be much less than when a solid film was deposited on a rock-salt plate. In order to correct for scatter by the solid film, the amplification was adjusted so that the recorder deflection at a wave-length where no bands are present was the same for the solid and the

liquid. Schematic diagrams of the spectra obtained for a number of different phenols are shown in the figures. The thick vertical lines correspond to the centre of the band, and the oblique lines give some indication of its width. The ordinates are in percentage absorption.

Discussion.—The results obtained for 12 phenols are summarised in the table. One of the most striking features of the spectra of the solids is the band splitting which occurs for 9 out of the 12 substances investigated. Certain bands which appear single in the spectrum of the liquid are split into two or even three components in that of the solid. These components can appear as sharply resolved doublets or as pronounced shoulders when the resolution is inadequate for complete separation. The cases in which this occurs are set out in cols. 1, 2, and 3 of the table. A few instances are found in which the reverse phenomenon occurs. For these exceptions, which are indicated by a negative sign in the table, well-marked doublets are not formed in going from solid to liquid, but a single band in the solid appears as a band plus a shoulder in the liquid. Col. 4 gives the cases in which a band plus a shoulder in the liquid appears as a doublet in the solid.

Summary of changes occurring in the infra-red spectra of alkylphenols in passing from the liquid to the solid state.

Substance.	1.	2.	3.	4.	5.	6.	7.	8.
Phenol	+1	+1 −1	+2 −1		+3	+5 −1	Several minor decreases	+ 1 −3
o-Cresol	+3		+3	+1	+1	+4	Several minor changes	+ 7 −3
p-Cresol	+1*	+2	+4			+4	Little change	+ 6 −2
p-Ethylphenol					+1	+1	1 Large decrease	+ 3 −5
o-3-Xylenol	+1		+1			+1	9 Large decreases	+11 −2
m-4-Xylenol	+1	+1	+2	+1		+2	Little change	+14 −0
p-Xylenol		−1	−1		+4	+4 −1	Several minor changes; 1 big decrease	+10 −2
m-2-Xylenol	+2		+2	+2		+2	Several minor decreases	+ 8 −3
o-4-Xylenol	+2	+2	+4	+1		+4	Little change	+ 4 −1
m-5-Xylenol	+3*	+3	+7			+7	3 Large decreases	+ 5 −3
4-Ethyl-*m*-cresol	+1		+1		+1	+1	Several minor increases	+ 7 −3
5-Ethyl-*m*-cresol		−1	−1		+1 −1	+1 −2	Several minor increases	+ 6 −2

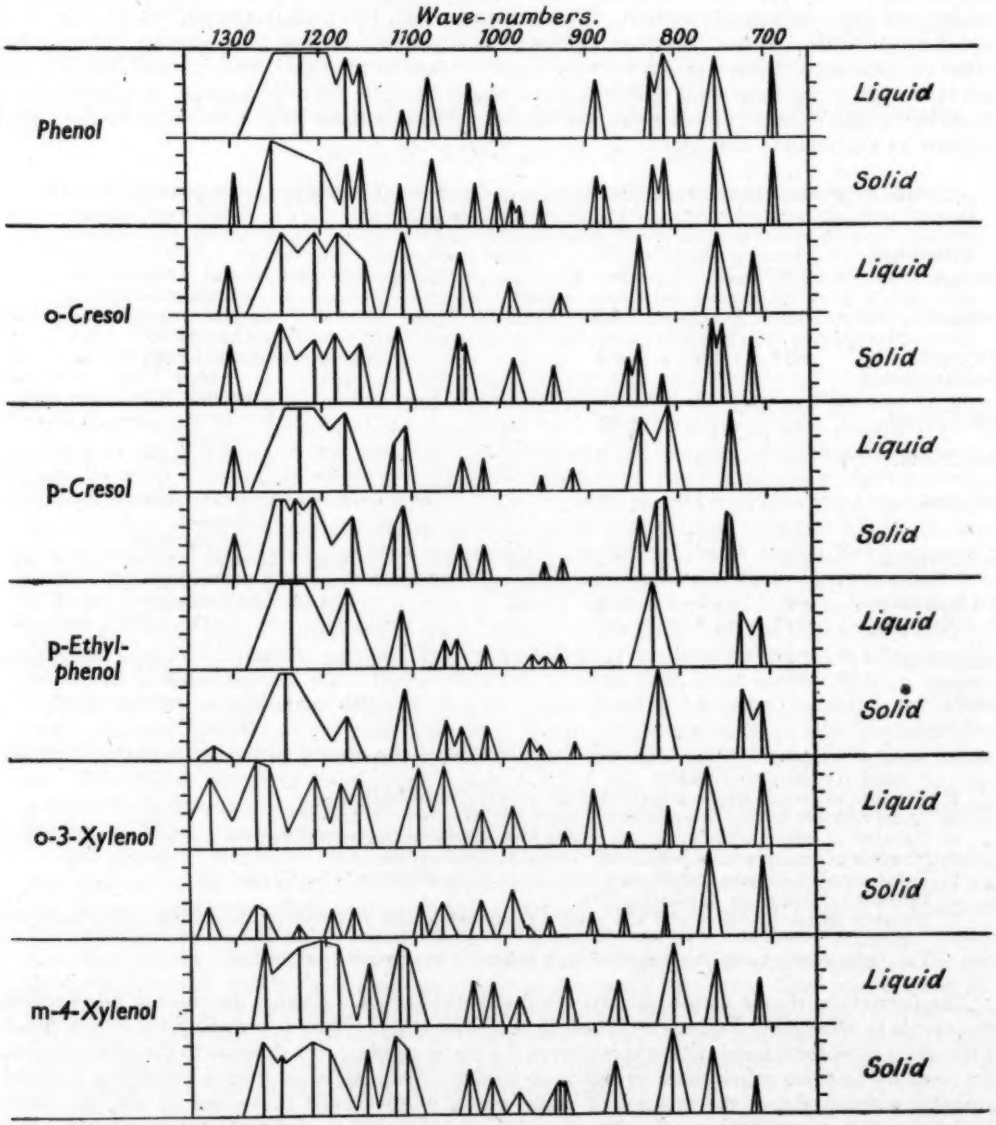
Col. 1. Number of bands which form doublets (or triplets) on crystallisation; * indicates that one band is split into a triplet.
„ 2. Number of bands which acquire shoulders on crystallisation.
„ 3. Total number of new frequencies formed by processes (1) and (2).
„ 4. Number of bands with shoulders which form doublets on crystallisation.
„ 5. Number of entirely new bands formed on crystallisation.
„ 6. Total number of new frequencies formed on crystallisation, *i.e.*, (3) and (5).
„ 7. Intensity changes on crystallisation.
„ 8. Number of bands for which the solid has higher (plus) or lower (minus) frequencies than the liquid.
Throughout the table the negative sign refers to the reverse process.

The formation of new bands can arise from several causes. First, a decrease in band width may result in effectively higher resolution in the solid state. This is probably the explanation of the cases in which a band with a shoulder in the liquid appears as a doublet in the solid (col. 4), and possibly in some other cases as well. A similar effect can arise from a reduction in band intensity accompanying the change of state which might result in values of the per cent. absorption more favourable for resolution. The latter effect is almost certainly operative in the region of strong absorption around 1200 wave-numbers and accounts for some of the cases listed in cols. 1 and 2—cf. *p*-cresol. Other possible explanations of the formation of new bands are that a splitting of the energy levels may occur or that a transition forbidden in one state may become allowed in another as a result of the influence of the crystal symmetry and give rise to a new band in the immediate vicinity of a band common to both states. Such new bands would not, however, be expected to be strong in molecular crystals.

The explanations we favour for the appearance of such well-defined doublets as are present

e.g., in crystalline *o*-cresol at *ca.* 750, 850, and 1040 wave-numbers, are different from any of those cited above. The first is that two isomers are possible for many xylenols arising out of the two possible positions of the OH bond directed towards or away from an *o*-methyl group (resonance confines the OH bond to the plane of the ring but does not specify its direction). Although these two isomeric forms are possible in the liquid one may predominate on grounds of stability. On the other hand, the nature of the packing in the crystal may require the formation

FIG. 1.

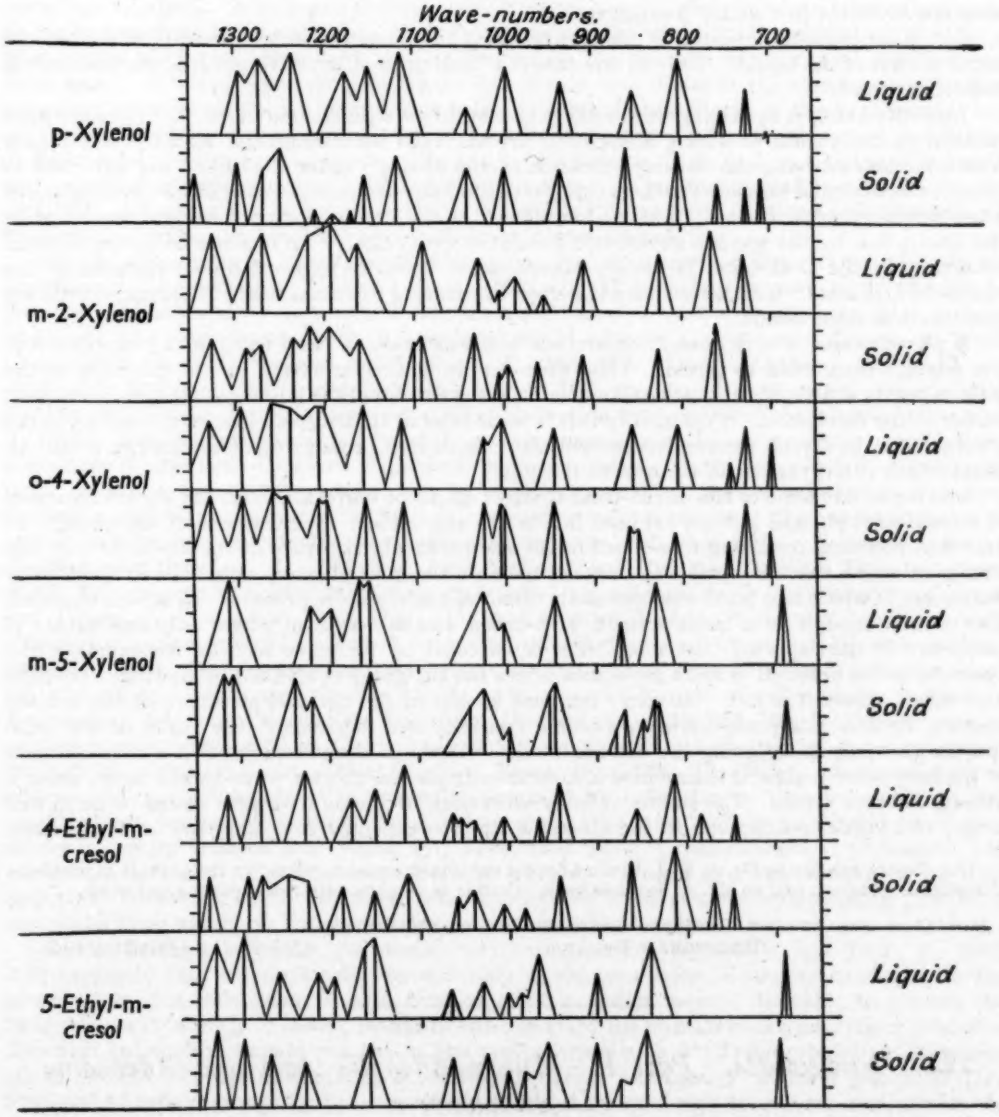


of a considerable proportion of the other. The second factor considered to be important is the occurrence in the unit cell of the crystal of two types of molecules differing in the nature of their environment. Even if all the molecules in the unit cell had the same isomeric form, it is highly probable that they could be classified according to their environment and these environmental effects are accentuated by the possibility of intermolecular hydrogen bonding. For example, some molecules in the unit cell may be packed in such a way that intermolecular hydrogen bonding may occur, while others may occupy positions in which such bonding is not possible.

It is noteworthy that the band in the region 730—840 wave-numbers, which has been interpreted as a deformation vibration involving the motion of the plane of the hydrogen atoms through the plane of the carbon atoms (Whiffen and Thompson, *J.*, 1945, 268), is sometimes split by the change from liquid to solid.

The absorption frequencies of corresponding bands in the solid and the liquid state usually differ by several wave-numbers, as can be seen from col. 8. In the great majority of cases the

FIG. 2.



frequency of the band in the solid is greater than that in the liquid. In previous work (Herzberg, " Infra-red and Raman Spectra of Polyatomic Molecules ", Van Nostrand, N.Y., 1945, p. 532) it has been found that when the position of a band is altered in going from liquid to solid, the shift is generally to longer wave-lengths. This is in direct contradiction to what has been found here. The explanation appears to be that previous work has been concerned with substances like hydrogen chloride and hydrogen sulphide which probably form associative bonds in the solid which tend to weaken the orginal valency bond and thus to decrease the frequency of

vibrations in which it is involved. In the present case two possible causes are suggested to account for the increase in frequencies observed. In the long-wave-length region in which we have worked many of the bands arise from deformation vibrations. Although hydrogen bonding decreases the frequency of the valency vibrations, it should have the reverse effect upon deformation vibrations. The other possible cause of frequency increase is the repulsive forces between the peripheral atoms of molecules which come into operation whenever the latter approach closer than their van der Waals radii. The magnitudes of the observed shifts are usually of the order of 5 wave-numbers, which is small in comparison with shifts arising from associative effects in valency frequencies.

Col. 5 contains the number of bands appearing in the spectrum of the solid which do not occur in that of the liquid. Only in one case is a band present in the liquid spectrum but not in that of the solid.

Intensity changes in passing from solid to the liquid are summarised in col. 7. They are most marked in the region of strong absorption around 1200 wave-numbers, which is the region where modes involving the valency vibration of the strongly polar C–O bond are expected to occur. Of particular note are the large changes of intensity occurring in *o*-3-, *p*-, and *m*-5-xylenols. They probably arise from the partial annulment of the dipole-moment changes concerned in the absorption by the specific association present in the crystal. An increase of dipole moment occurring in the C–O bond is always accompanied by a decrease of dipole moment of the *associated* OH bond. This would have the effect of reducing the intensities of the bands involving vibrations in these bonds.

A phenomenon of very general occurrence is the decrease in band width which accompanies the passage from solid to liquid. This often results in the resolution in the spectrum of the solid of bands which only appear as shoulders in the spectrum of the liquid, as has been mentioned earlier in the discussion. Presumably this is to be related to the greater order prevailing in the crystal. In the liquid, intermolecular collisions result in a broadening of the energy levels, an effect which is not present in the case of the solid.

The hope that some of the liquid–solid changes might be correlated with the known structure of the different phenols has not yet been fulfilled to any extent. For instance, it was thought at first that doubling occurring in *o*-cresol might arise from the presence in the liquid of only one isomer in which the OH bond was directed towards the methyl group, and that in the crystal the isomer in which this bond was oppositely directed might also be present. However, doubling also occurs, though to a lesser extent, in *p*-cresol and *m*-5-xylenol where only one isomer is possible. It thus appears that some other cause must be operative such as, for example, the presence in the unit cell of some molecules where the CO group is affected by hydrogen bonding and others where it is not. As more becomes known of the detailed structure of the xylenol spectra, further interpretation may become possible, and conversely, the study of the solid spectra may help in assigning the various bands. Although the present work has been confined to the long-wave region, it is intended also to investigate the shorter wave-length range, using a lithium fluoride prism. The simple valency vibrations involving hydrogen atoms occur in this range, and important changes in the spectrum may be expected to accompany crystallisation.

Our thanks are due to Dr. A. E. J. Vickers for his continued encouragement in the pursuit of problems of academic interest, and to Mr. A. Sumner for invaluable assistance with the experimental work.

RESEARCH DEPARTMENT, IMPERIAL CHEMICAL INDUSTRIES LIMITED,
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122. *Nucleotides. Part I. Muscle Adenylic Acid and Adenosine Diphosphate.*

By J. BADDILEY and A. R. TODD.

Muscle adenylic acid (adenosine-5′ phosphate) can be prepared in good yield by treatment of 2′ : 3′-*iso*propylidene adenosine with dibenzyl chlorophosphonate followed by removal of the benzyl and *iso*propylidene residues. 2′ : 3′-iso*Propylidene adenosine-5′ dibenzyl phosphate*, an intermediate in this preparation, can be converted by careful hydrolysis into *adenosine-5′ benzyl phosphate*. From this a synthesis of *adenosine-5′ pyrophosphate*, identical with natural adenosine diphosphate, has been effected by reaction of its silver salt with dibenzyl chlorophosphonate and subsequent debenzylation of the product.

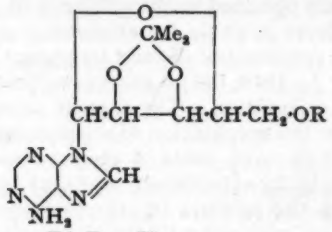
DURING recent years an extended series of investigations has been in progress in this laboratory having as its object the application of synthetic methods to the study of nucleotides. In a series of papers in this *Journal* we have reported results obtained in the synthesis of nucleosides and on the development of phosphorylation procedures suitable for application to sensitive molecules and offering the possibility of extension to synthesis of di- and tri-phosphoric esters. In a lecture recently delivered to the Society (Todd, *J.*, 1946, 647) a general review was given of the progress of these investigations and of their orientation. The present paper contains the initial results obtained in applying our methods to the preparation of nucleotides exercising coenzyme function. It is hoped that as a result of such work some of these nucleotides may be made more readily accessible and their structures rigidly established, and that by the study of synthetic analogues some light may be thrown on the problem of structural specificity in coenzymes. It is also clear that studies of this nature may assist in the clarification of some important aspects of polynucleotide structure. Given the structure of the nucleosides, the synthesis of nucleotides in general comprises three basic problems : (*a*) effective phosphorylation of nucleosides, (*b*) synthesis of esters of di- and tri-phosphoric acids, and (*c*) linkage of different molecules through phosphate or polyphosphate residues. In our initial studies muscle adenylic acid (III) and adenosine diphosphate (VI) were selected as compounds whose partial synthesis from natural adenosine involved a solution of problems (*a*) and (*b*).

Muscle adenylic acid (adenosine-5′ phosphate) was first isolated from rabbit muscle by Embden and Zimmermann (*Z. physiol. Chem.*, 1927, **167**, 137), and the location of the phosphate group was determined by degradation (Levene and Mori, *J. Biol. Chem.*, 1929, **81**, 215). Since adenosine has been shown to be 9-β-*d*-ribofuranosidoadenine (Levene and Tipson, *J. Biol. Chem.*, 1932, **94**, 809; Gulland and Holiday, *J.*, 1936, 765; Davoll, Lythgoe, and Todd, *J.*, 1946, 833; Lythgoe, Smith, and Todd, this vol., p. 355), the structure of muscle adenylic acid may be regarded as completely defined. This nucleotide is of considerable interest because of its role in muscle contraction and its effect on the heart and on blood pressure; preparations containing it have been employed clinically from time to time. It has been partially synthesised from adenosine by several workers, but in yields so poor that the nucleotide has remained accessible only by fermentative methods or by extraction from muscle. The synthetic methods employed have been direct phosphorylation of adenosine with phosphoryl chloride in pyridine (Jachimowicz, *Biochem. Z.*, 1937, **292**, 356; Gulland and Hobday, *J.*, 1940, 746), treatment of 2′ : 3′-*iso*propylidene adenosine with phosphoryl chloride followed by hydrolysis (Levene and Tipson, *J. Biol. Chem.*, 1937, **121**, 131), and treatment of 2′ : 3′-diacetyl adenosine with diphenyl chlorophosphonate followed by hydrolysis (Bredereck, Berger, and Ehrenberg, *Ber.*, 1940, **73**, 269); the last two methods being unambiguous as regards point of attachment of the phosphate residue confirm the allotted structure of muscle adenylic acid. Adenosine diphosphate was first obtained by Lohmann (*Biochem. Z.*, 1935, **282**, 109) by the action of a washed muscle preparation on adenosine triphosphate, and it has been isolated as a degradation product of cozymase (Vestin, Schlenk, and v. Euler, *Ber.*, 1937, **70**, 1369). Its formulation as adenosine-5′ pyrophosphate (VI), originally proposed by Lohmann on titration evidence, has recently been verified by Lythgoe and Todd (*Nature*, 1945, **155**, 695) by a periodate oxidation method, and by Gulland and Walsh (*J.*, 1945, 169) using a combination of titrimetric and enzymatic methods. So far no synthesis or partial synthesis has been described for this important nucleotide which functions in transphosphorylation systems by accepting phosphate and undergoing reversible transformation to adenosine triphosphate.

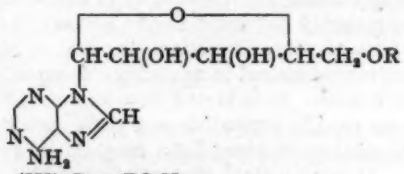
Earlier model experiments on phosphorylation (Atherton, Openshaw, and Todd, *J.*, 1945, 382) suggested that dibenzyl chlorophosphonate would be a suitable reagent to employ in the preparation of muscle adenylic acid from adenosine, and it seemed desirable to protect the hydroxyls at C_2' and C_3' in the nucleoside in order to avoid the formation of a mixture of products. Dibenzyl chlorophosphonate reacted at low temperature with 2′ : 3′-*iso*propylidene adenosine (I) in presence of pyridine giving 2′ : 3′-iso*propylidene adenosine-5′ dibenzyl phosphate* (II). Removal of benzyl groups by hydrogenolysis, followed by mild acid treatment to eliminate the acetone residue, gave adenosine-5′ phosphate, identical with muscle adenylic acid isolated from natural sources. Attention is drawn to the overall yield from adenosine (45%), which makes the nucleotide a comparatively accessible product.

The observation that organic pyrophosphates can be conveniently prepared by condensing a metallic salt of a diester of phosphoric acid with a halogeno-phosphonate, made in the course of other work by Mr. F. R. Atherton, suggested that 2′ : 3′-*iso*propylidene adenosine-5′ dibenzyl phosphate would be a suitable starting material for the preparation of adenosine diphosphate, since partial debenzylation would give a diester of phosphoric acid. One method of achieving

this object seemed to be controlled hydrogenolysis of (II), since this has been shown to be practicable with dibenzyl *iso*amyl phosphate (Atherton, Openshaw, and Todd, *loc. cit.*). It



(I.) R = H.
(II.) R = $PO(O{\cdot}CH_2Ph)_2$.



(III) R = PO_3H_2.
(IV.) R = $PO(OH){\cdot}O{\cdot}CH_2Ph$.
(V.) R = $PO(O{\cdot}CH_2Ph){\cdot}O{\cdot}PO(O{\cdot}CH_2Ph)_2$.
(VI.) R = $PO(OH){\cdot}O{\cdot}PO(OH)_2$.

was felt, however, that retention of the acetone residue during the projected synthesis would be undesirable, since its removal without fission of a pyrophosphate linkage might present difficulty. Accordingly, careful hydrolysis of (II) with dilute acid was carried out instead of hydrogenolysis. Under suitable conditions the acetone residue was removed together with one benzyl group giving *adenosine-5′ benzyl phosphate* (IV), which readily formed a silver salt. It was difficult to find a suitable solvent for the reaction of this salt with dibenzyl chlorophosphonate, but in warm glacial acetic acid reaction occurred smoothly with separation of silver chloride. The product, presumably adenosine-5′ tribenzyl pyrophosphate (V), was a brittle resin; catalytic hydrogenation in alcoholic solution gave *adenosine-5′ pyrophosphate* (VI), conveniently isolated as its *acridine* salt, which proved identical with the acridine salt of natural adenosine diphosphate.

Extension of this work with a view to the synthesis of adenosine triphosphate and other nucleotide coenzymes is in progress.

Experimental.

2′ : 3′-iso Propylidene Adenosine.—Levene and Tipson (*loc. cit.*) record for this substance m. p. 200—204° after softening at 190°, and $[\alpha]_D^{20°}$ −63·9°. Our product prepared by their method melted sharply at 220° without previous softening and had $[\alpha]_D^{18°}$ −65·0° (*c*, 1 in water) (Found: C, 50·9; H, 5·8; N, 23·0. Calc. for $C_{13}H_{17}O_4N_5$: C, 50·7; H, 5·5; N, 22·8%).

2′ : 3′-iso Propylidene Adenosine-5′ Dibenzyl Phosphate.—2′ : 3′-*iso*Propylidene adenosine (5 g. dried for 24 hours at 116°/10^{-3} mm.) was dissolved by warming in dry pyridine (60 c.c.) and the solution cooled in an acetone–solid carbon dioxide bath until the liquid at the sides of the flask began to solidify. Dibenzyl chlorophosphonate [prepared according to Atherton, Openshaw, and Todd (*loc. cit.*) by chlorinating 12 g. of dibenzyl phosphite in carbon tetrachloride solution and removing solvent under reduced pressure below 30°] was added rapidly with shaking and the mixture left for 3 hours in the cold bath at a temperature just above the freezing point of the mixture and then set aside at room temperature overnight. Water (20 c.c.) and sodium carbonate (*ca.* 5 g.) were added and the solution was evaporated under reduced pressure. The syrup so obtained was dissolved in chloroform (100 c.c.), and the solution washed thoroughly with water containing a small amount of sodium hydrogen carbonate, then with water, dried, and evaporated. After the residual syrup had been twice evaporated with alcohol to remove any traces of solvent, it was dissolved in a minimum amount of alcohol and treated with ether until slightly turbid. On standing at 0° for several hours, or more rapidly by seeding, the product separated in crystalline form. Recrystallised from alcohol–ether, *2′ : 3′-iso propylidene adenosine-5′ dibenzyl phosphate* formed small, colourless needles (4·8 g.; 52%), m. p. 97—98° (Found in material dried at 50°: C, 57·0; H, 5·4; N, 12·4. $C_{27}H_{30}O_7N_5P$ requires C, 57·0; H, 5·3; N, 12·4%).

Adenosine-5′ Phosphate (Muscle Adenylic Acid).—2′ : 3′-*iso*Propylidene adenosine-5′ dibenzyl phosphate (0·7 g.) was dissolved in aqueous alcohol (50 c.c. of 50%) and shaken with hydrogen at atmospheric pressure using an Adams's palladium oxide catalyst; absorption of hydrogen was rapid, the theoretical amount for removal of two benzyl groups being taken up in 10 minutes. The catalyst was removed by filtration, the solution evaporated to dryness under reduced pressure, the residue dissolved in dilute sulphuric acid (100 c.c. of 0·1N), and the solution set aside for 2 days to hydrolyse the *iso*propylidene residue. The sulphuric acid was neutralised with the calculated amount of barium hydroxide, barium sulphate spun off, and the solution concentrated to small bulk. On standing overnight at 0° adenosine-5′ phosphate crystallised in fine needles (0·35 g.; 85%), m. p. 190°, undepressed in admixture with authentic muscle adenylic acid (m. p. 192°). Recrystallised from water it forms a dihydrate (Found in material dried at room temperature: C, 31·6; H, 5·0; N, 18·1; loss at 110°, 9·5. Calc. for $C_{10}H_{14}O_7N_5P,2H_2O$: C, 31·3; H, 4·9; N, 18·3; H_2O, 9·4%. Found in material dried at 110°: C, 34·3; H, 4·0; P, 8·7. Calc. for $C_{10}H_{14}O_7N_5P$: C, 34·6; H, 4·0; P, 8·9%). The acridine salt of the synthetic compound had m. p. 208°, undepressed by the acridine salt of natural muscle adenylic acid (m. p. 208°). The synthetic product had $[\alpha]_D^{20°}$ −45·5° (*c*, 0·72 in water) and the natural $[\alpha]_D^{20}$ −46·4° (*c*, 0·56 in water).

Adenosine-5′ Benzyl Phosphate.—2′ : 3′-*iso*Propylidene adenosine-5′ dibenzyl phosphate (5·4 g.) was dissolved in a mixture of dilute sulphuric acid (500 c.c. of N/50) and alcohol (150 c.c.) and the solu-

tion refluxed for 1 hour. Sulphate was removed by adding the calculated amount of barium hydroxide, the precipitated barium sulphate being removed by filtration. Concentrated to small bulk and set aside at room temperature, the solution deposited *adenosine-5′ benzyl phosphate*, which recrystallised from water as colourless needles (3·7 g.; 90%), m. p. 234° (decomp.) (Found in material dried at 110° C, 46·3; H, 4·8; N, 16·3. $C_{17}H_{20}O_7N_5P$ requires C, 46·5; H, 4·6; N, 16·1%). The *silver* salt was precipitated as a white powder on adding silver nitrate to a solution of substance in the requisite amount of aqueous sodium hydroxide. On catalytic hydrogenation, adenosine-5′ benzyl phosphate rapidly took up 1 mol. of hydrogen yielding muscle adenylic acid, identified by m. p. and mixed m. p. (208°) of its acridine salt.

Adenosine-5′ Pyrophosphate (*Adenosine Diphosphate*).—Dibenzyl chlorophosphonate (from 7 g. of dibenzyl phosphite) was added to a suspension of silver adenosine-5′ benzyl phosphate (4·2 g. dried for 24 hours at 116°/10^{-3} mm.) in anhydrous acetic acid (120 c.c.) at 50—60°. The mixture was shaken for 30 minutes, during which time the silver salt gradually disappeared and was replaced by silver chloride. The mixture was left overnight in the dark and then filtered, and the filtrate evaporated under reduced pressure. The residue was evaporated thrice with alcohol and triturated with ether; it then formed a brittle resin which could not be crystallised. This resinous product was dissolved in aqueous alcohol (100 c.c. of 50%) and hydrogenated at ordinary temperature and pressure using a palladium oxide catalyst. Hydrogenation was complete in 6 hours. Catalyst was removed by filtration and the filtrate concentrated to one-third volume under reduced pressure and decanted from a small amount of oil which separated. An equal volume of alcohol was then added, and aqueous barium hydroxide added to pH 8·5. The precipitated barium salt was collected by centrifugation, washed with aqueous alcohol (50%), and dried (yield, 5·1 g.).

The crude barium salt (5 g.) was suspended in a little water and dilute sulphuric acid (23·8 c.c. of N) added. Precipitated barium sulphate was spun off and washed with water, and the combined supernatant liquid and washings were treated with alcoholic acridine (1·1 g. in 50 c.c.). On standing, the *acridine* salt of adenosine-5′ pyrophosphate separated. Recrystallised from water it formed characteristic yellow prismatic needles (0·8 g.; 18%), m. p. 215° (decomp.), undepressed in admixture with an authentic sample of the acridine salt of natural adenosine diphosphate (m. p. 215° decomp.) prepared according to Wagner-Jauregg (*Z. physiol. Chem.*, 1936, **239**, 188) (Found in material dried at 110°: C, 44·9; H, 4·1; N, 13·5; P, 9·8. $C_{16}H_{15}O_{10}N_5P_2,C_{13}H_9N$ requires C, 45·5; H, 4·0; N, 13·9; P, 10·2%). Determination of acid-labile phosphorus (*i.e.*, phosphorus removed in 15 minutes at 100° with N-hydrochloric acid) and total phosphorus in a solution of adenosine diphosphate prepared from the synthetic acridine salt gave a ratio, acid-labile P/total P = 1·01/2 (calculated ratio for adenosine diphosphate = 1/2); these estimations were made using the colorimetric method of Allen (*Biochem. J.*, 1940, **34**, 858). For further confirmation of identity, the acridine salts of natural and synthetic adenosine diphosphate were examined by Dr. Clews and Mr. Nicol of the Department of Crystallography; *X*-ray powder photographs of the two materials were indistinguishable from one another.

We are grateful to Roche Products Ltd. for gifts of material, and to Dr. K. Bailey for the gift of a sample of barium adenosine diphosphate prepared from muscle.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 22nd*, 1946.]

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123. *The Formation of Phenanthroxazole by the Action of Diazomethane on Phenanthraquinoneimine.*

By ALEXANDER SCHÖNBERG AND WILLIAM IBRAHIM AWAD.

Phenanthraquinoneimine (I; R′ = R″ = H) when treated with diazomethane yields phenanthroxazole (IV; R = R′ = R″ = H). The action of diazoethane yields 2-methylphenanthroxazole (IV; R = Me, R′ = R″ = H). Retenequinoneimine (I; R′ = Me or Pr$^\beta$, R″ = Pr$^\beta$ or Me) behaves similarly.

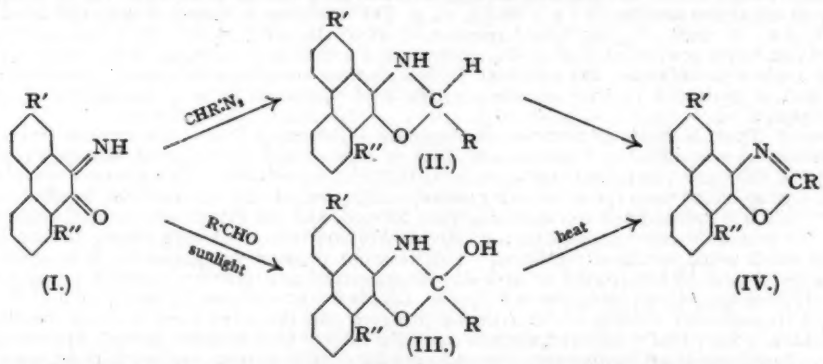
Retenequinoneimine in sunlight with acetaldehyde, benzaldehyde, or anisaldehyde yields the substances (III; R = Me, Ph, or C_6H_4·OMe; R′ and R″ as above); the first, on being heated, yields 2-methylreteneoxazole (IV; R = Me; R′ and R″ as above), identical with the product obtained by the action of diazoethane on retenequinoneimine. Similarly, 2-hydroxy-2-methyl-2 : 3-dihydrophenanthroaxazole (III; R = Me, R′ = R″ = H) gives 2-methylphenanthroxazole (IV; R = Me, R′ = R″ = H) on heating, identical with the product obtained from diazoethane and phenanthraquinoneimine.

The product obtained by De and Ghosh by the action of formic acid on 9-amino-10-phenanthrol hydrochloride and described as phenanthroxazole proved to be phenanthroxazine (V).

As far as we are aware, the formation of oxazoles by the method mentioned above or by similar reactions has not hitherto been observed.

When phenanthraquinoneimine (I; R′ = R″ = H) was treated with diazomethane, phenanthroxazole (IV ; R = R′ = R″ = H) was obtained and identified by comparison with an authentic sample (Pschorr, *Ber.*, 1902, **35**, 2740). It is believed that the first step in this reaction is the formation of 2 : 3-dihydrophenanthroxazole (II; R = R′ = R″ = H) which, in consequence of oxidation, yields the oxazole: atmospheric oxygen or phenanthra-

quinoneimine itself, which is readily reduced to 9-amino-10-phenanthrol (McCoy and Day, *J. Amer. Chem. Soc.*, 1943, **65**, 1956), may serve as oxidising agent.

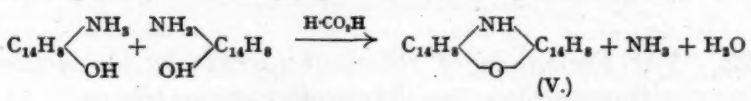


The action of diazoethane on phenanthraquinoneimine yielded *2-methylphenanthroxazole* (IV; R = Me, R′ = R″ = H), the constitution of which was proved by a second synthesis. Phenanthraquinoneimine and acetaldehyde in sunlight yielded 2-hydroxy-2-methyl-2 : 3-dihydrophenanthroxazole (III; R = Me, R′ = R″ = H) (cf. Schönberg and Awad, *J.*, 1945, 197), which on heating lost water with the formation of the oxazole (as IV), proved to be identical with the product obtained by the action of diazoethane on phenanthraquinoneimine.

The action of diazomethane on retenequinoneimine * yielded reteneoxazole (IV; R = H, R′ = Me and R″ = Pr^{β} or conversely), and diazoethane similarly gave 2-methylreteneoxazole (IV; R = Me, R′ = Me, R″ = Pr^{β}, etc.), the latter also being obtained by the action of acetaldehyde, followed by heat, on the imine.

We have also prepared by the same method from benzaldehyde and anisaldehyde *2-hydroxy-2-phenyl-2 : 3-dihydroreteneoxazole* and its *2-anisyl* analogue, respectively, of type (III).

De and Ghosh stated (*J. Ind. Chem. Soc.*, 1930, **7**, 357) that they obtained phenanthroxazole by interaction of 9-amino-10-phenanthrol hydrochloride and formic acid; they described it as a brown substance, m. p. >300°, but did not give analyses for carbon and hydrogen. Such a high m. p. and deep colour are highly improbable for phenanthroxazole. Moreover, those authors did not mention that Pschorr (*loc. cit.*) had already prepared this oxazole. We believe the substance to be phenanthroxazine (V), produced according to the scheme :



De and Ghosh also stated that they obtained 2-methylphenanthroxazole by the use of acetic acid instead of formic acid. As the substance is brown with m. p. >300°, such a constitution is improbable. The true 2-methylphenanthroxazole is described above.

Experimental.

Action of Diazomethane.—(a) *On phenanthraquinoneimine.* The imine, suspended in dry ether, was treated in the cold with an ethereal solution of excess of diazomethane (prepared from nitrosomethylurea and aqueous potassium hydroxide). The product was crystallised from methyl alcohol (charcoal) and phenanthroxazole was obtained in light yellow crystals, m. p. 152°, subliming unchanged in a vacuum [Found : C, 82·0; H, 4·2; N, 6·4; *M* (Rast's method), 216. Calc. for $C_{15}H_9ON$: C, 82·2; H, 4·1; N, 6·4%; *M*, 219]. A mixed m. p. with phenanthroxazole prepared according to Pschorr (*loc. cit.*) gave no depression. (Pschorr reported a brownish-yellow product of m. p. 146.°) In the preparation, we followed Pschorr's method, but found it advisable to use 10% sodium hydroxide solution in the methylation of phenanthraquinone monoxime.

(b) *On retenequinoneimine.* The reaction was carried out as above. Reteneoxazole crystallised from methyl alcohol in yellow crystals, m. p. 108° (Jaffe and Day, *J. Org. Chem.*, 1943, **8**, 43, gave m. p. 108°) (Found : C, 82·7; H, 6·1; N, 5·3. Calc. for $C_{19}H_{17}ON$: C, 82·9; H, 6·2; N, 5·1%).

Action of Diazoethane (Werner, *J.*, 1919, **115**, 1093).—(a) *On phenanthraquinoneimine.* The reaction was carried out as with diazomethane and the product was crystallised from methyl alcohol; *2-methylphenanthroxazole* forms light yellow crystals, m. p. 145°. It gives no colour reaction with concentrated sulphuric acid and is insoluble in dilute sodium hydroxide or dilute hydrochloric acid, in both cases

* The constitution of this imine is uncertain; hence the alternatives for R′ and R″ to correspond with uncertainty in the relative positions of :NH and :O.

in the cold as well as on boiling. It is soluble in boiling benzene (Found: C, 82·2; H, 5·1; N, 6·5. $C_{16}H_{11}ON$ requires C, 82·4; H, 4·7; N, 6·0%).

(b) *On reteneguinoneimine.* 2-Methylretenoxazole (IV; R = Me, R′ or R″ = Me or Pr$^{\beta}$) was obtained from methyl alcohol in almost colourless crystals, m. p. 135°: Jaffe and Day (*loc. cit.*) gave m. p. 127·5—128·5°. The substance dissolves in concentrated sulphuric acid with a light yellow colour (Found: C, 82·8; H, 6·45; N, 5·0. Calc. for $C_{20}H_{19}ON$: C, 83·0; H, 6·6; N, 4·8%).

Action of Alcoholic Hydrochloric Acid.—(a) *On phenanthroxazole.* 0·1 G. of phenanthroxazole was refluxed with a mixture of 20 c.c. of alcohol and 10 c.c. of hydrochloric acid for 3 hours; on cooling and concentration, orange crystals of phenanthraquinone appeared. It is probable that the above reaction first yields 9-amino-10-phenanthrol, and that this is then changed into 9 : 10-dihydroxyphenanthrene, which is oxidised by the air to phenanthraquinone. We have satisfied ourselves that 9-amino-10-phenanthrol, when treated with alcoholic hydrochloric acid under the conditions mentioned above, yields phenanthraquinone. Furthermore, the aminophenanthrol has been obtained by Pschorr (*loc. cit.*) by the action of hydrochloric acid on phenanthroxazole.

(b) *On reteneoxazole.* The reaction was carried out as above, and retenequinone obtained.

Action of Aldehydes on Retenequinoneimine in Sunlight.—General remarks. The photochemical reactions were carried out in Monax-glass tubes, the air being displaced by dry carbon dioxide, and the tubes sealed by fusion. The benzene was thiophen-free and dried over sodium.

(a) *With benzaldehyde.* Retenequinoneimine (0·5 g.) and benzaldehyde (1 g.) in 50 c.c. of benzene were exposed to sunlight for 2 days (January), the benzene was driven off in a vacuum, and the product repeatedly crystallised from alcohol, in which it is difficultly soluble in the cold; *2-hydroxy-2-phenyl-2 : 3-dihydroreteneoxazole* (III; R = Ph, R′, R″ = Me, Pr$^{\beta}$) forms almost colourless crystals, m. p. about 168°, with decomposition and a red brown melt (Found: N, 3·8. $C_{21}H_{23}O_2N$ requires N, 3·8%).

(b) *With anisaldehyde.* Retenequinoneimine (0·5 g.) and anisaldehyde (1 g.) in 50 c.c. of benzene were left for one month (February—March). *2-Hydroxy-2-anisyl-2 : 3-dihydroreteneoxazole* separated out during the experiment in the form of crystals. It recrystallised from benzene as pale yellow crystals, m. p. 222°, with evolution of gas (Found: C, 77·9; H, 6·1; N, 3·7. $C_{28}H_{25}O_3N$ requires C, 78·2; H, 6·3; N, 3·5%).

(c) *With acetaldehyde.* 0·5 G. of retenequinoneimine and 10 g. of acetaldehyde in 50 c.c. of benzene were exposed for 5 days (April) to sunlight. The product was crystallised from benzene–alcohol, giving almost colourless crystals, m. p. 130°. This substance was pyrolysed for 30 minutes in a stream of dry carbon dioxide, the vessel being immersed in a bath of ethyl cinnamate (b. p. 271°) and fitted with a long side tube externally cooled. The product, which formed crystals on the cold part of the reaction vessel, was crystallised from methyl alcohol; its m. p. of 135° was not depressed on admixture with 2-methyl-reteneoxazole obtained by the action of diazoethane on retenequinoneimine (Found: N, 5·0. Calc. for $C_{20}H_{19}ON$: N, 4·8%).

Pyrolysis of 2-Hydroxy-2-methyl-2 : 3-dihydrophenanthroxazole.—This was carried out as described above. 2-Methylphenanthroxazole was obtained; it crystallised from methyl alcohol and had m. p. and mixed m. p. with the product obtained by the action of diazoethane on phenanthraquinoneimine 145° (Found: C, 81·8; H, 4·7; N, 5·6. Calc. for $C_{16}H_{11}ON$: C, 82·4; H, 4·7; N, 6·0%).

Action of Chromium Trioxide on 2-Hydroxy-2-anisyl-2 : 3-dihydroreteneoxazole.—To the reteneoxazole derivative (0·4 g.) in 50 c.c. of glacial acetic acid, a solution of 0·4 g. of chromium trioxide in 10 c.c. of glacial acetic acid was added, and the mixture heated for 2 hours and then cooled. Water was added, and the precipitate proved to be retenequinone after crystallisation from alcohol–chloroform.

Action of Formic Acid on 9-Amino-10-phenanthrol Hydrochloride.—The experiment was carried out as described by De and Ghosh (*loc. cit.*). The brown product which separated during heating was isolated and purified by repreated extraction with alcohol; m. p. above 350°. It showed a violet colour with concentrated sulphuric acid (Found: N, 4·0. Calc. for $C_{28}H_{17}ON$: N, 3·7%). Phenanthroxazine was also purified by vacuum sublimation, giving green crystals which became brown after pulverisation (cf. Bamberger and Grob, *Ber.*, 1901, **34**, 533) (Found: N, 3·2. Calc. for $C_{28}H_{17}ON$: N, 3·7%)

FOUAD I UNIVERSITY, ABBASSIA, CAIRO. [*Received, August 23rd,* 1946.]

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124. *The Preparation and Properties of Thionaphthindoles.*

By CHARLES E. DALGLIESH and FREDERICK G. MANN.

The condensation of various thioindoxyls with phenylhydrazine and substituted phenylhydrazines has been investigated. This condensation gives thionaphthindoles very readily by the Fischer indole reaction. It is now found, however, that the formation of the thionaphthindoles is apparently completely inhibited by 4-substituents in the thioindoxyls and by ortho-substituents in the phenylhydrazines. The significance of these results is discussed.

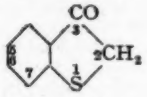
Several thionaphthindoles having additional fused rings have been synthesised: these compounds resemble in general molecular structure certain carcinogenic polycyclic aromatic hydrocarbons, and their therapeutic properties are therefore under investigation.

IT has been shown by McClelland and D'Silva (*J.*, 1932, 227) that when thioindoxyl (I) is warmed with phenylhydrazine in acetic acid solution, the intermediate phenylhydrazone very readily undergoes the Fischer indole reaction with the formation of thionaphthindole (II),* the structure

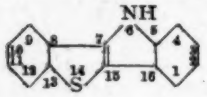
* The numbering of (II) is that used by McClelland and D'Silva (*loc. cit.*) and differs from that adopted in " The Ring Index " (Patterson and Capell, 1940).

of which had been proved by McClelland (*J.*, 1929, 1588). It was found that 5-methylthioindoxyl similarly gave 10-methylthionaphthindole, and that the reaction also proceeded readily when thioindoxyl was treated with certain substituted phenylhydrazines. These authors concluded therefore that the reaction was general. Subsequently 5-chlorothioindoxyl was found to give 10-chlorothionaphthindole (Fowkes and McClelland, *J.*, 1941, 187). No application of this reaction to thioindoxyls other than the above three has been recorded.

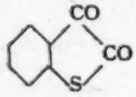
We have investigated the nature and scope of this reaction for two reasons. First, Dalgliesh and Mann (*J.*, 1945, 893) have condensed a number of substituted thioindoxyls (as I) with



(I.)



(II.)

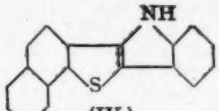


(III.)

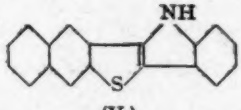
similar thionaphthenquinones (as III) to ascertain the factors which determined whether the methylene group of the thioindoxyls condensed with the α(or 2)-carbonyl group of the quinones to form a thioindigo, or with the β(or 3)-carbonyl group to form a thioindirubin. In the majority of the condensations studied, the β-carbonyl group of the thionaphthenquinone reacted, but such a condensation appeared to be inhibited almost invariably by a 4-substituent in thionaphthenquinone. The reasons why these 4-substituted quinones thus gave solely thioindigos by α-carbonyl condensation were discussed, and evidence was adduced that steric hindrance by the 4-substituent was probably the main cause. In McClelland's thionaphthindole synthesis, the intial reaction is necessarily the condensation of the reactive amino-group of the phenylhydrazine with the 3-carbonyl group of the thioindoxyl (as such or in its enol form), and it was of some interest therefore to determine whether this reaction was also markedly affected by the presence of 4-substituents.

Secondly, it is clear that the use of various benzthioindoxyls and of naphthylhydrazines should result in thionaphthindoles containing additional fused rings, and these polycyclic derivatives would bear a structural resemblance to polycyclic hydrocarbons known to possess carcinogenic properties (*vide infra*). The synthesis of such compounds was therefore investigated.

We found that the following thioindoxyls readily gave the corresponding thionaphthindoles: thioindoxyl, and 5-chloro-7-methyl-, 6-ethoxy-, 6 : 7-benz-, 5 : 6-benz-, 5-methyl-, 7-methyl-, and 7-chloro-thioindoxyl.* The hydrazines used for condensation with these thioindoxyls included phenyl-, *p*-nitrophenyl-, *p*-tolyl-, *m*-tolyl-, 1-phenyl-2-methyl-, and 1-phenyl-2-ethyl-hydrazine, and 1-amino-1 : 2 : 3 : 4-tetrahydroquinoline. These reactions proceeded so readily that the resulting thionaphthindoles formed excellent crystalline derivatives for the



(IV.)



(V.)

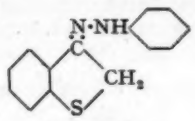
characterisation of the parent thioindoxyls. The use of 6 : 7- and 5 : 6-benzthioindoxyl gave two new ring systems, 11 : 12- (IV) and 10 : 11-*benzthionaphthindole* (V). The new ring systems obtained by the use of the aminoquinoline are described later.

It is noteworthy that no thionaphthindole could be detected in the reaction products of the following pairs: (A) phenylhydrazine with 6-chloro-4-methyl-, 4 : 5-benz-, 4-chloro-, and 4 : 7-dichloro-thioindoxyl; (B) thioindoxyl with 2 : 4-dinitrophenyl-, *o*-tolyl- and α-naphthyl-hydrazine, or 6 : 7-benzthioindoxyl with *o*-tolylhydrazine. Each pair in class (A) includes a thioindoxyl carrying a 4-substituent, whereas each in class (B) includes a phenylhydrazine carrying an ortho-substituent. All these reaction products appeared to be complex, and usually tarry, mixtures and were in striking contrast to the highly crystalline thionaphthindoles which resulted from the earlier reactions.

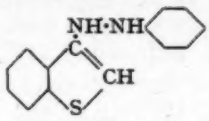
The mechanism of the formation of thionaphthindoles from thioindoxyls has been discussed by McClelland and D'Silva (*loc. cit.*), who pointed out that the properties of the thioindoxyl molecule are peculiarly favourable for indolisation of the hydrazone to occur by the mechanism of the Fischer indole reaction proposed by Robinson and Robinson (*J.*, 1918, **113**, 639; 1924,

* For purpose of comparison, these thioindoxyls are cited throughout this paper in the order given by Dalgliesh and Mann (*loc. cit.*).

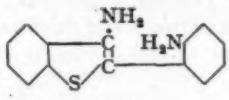
125, 827). This mechanism in the present case would involve the isomerisation of the hydrazone (VI) to the hydrazino-compound (VII), followed by an *o*-benzidine rearrangement to give



(VI.)



(VII.)

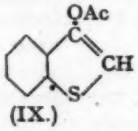


(VIII.)

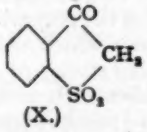
the diamine (VIII), which would finally lose ammonia, possibly by the mechanism suggested by Allen and Wilson (*J. Amer. Chem. Soc.*, 1943, **65**, 611), to form the thionaphthindole (II).

It is clear therefore that at least one stage of this mechanism must be inhibited by 4-substituents in the thioindoxyl and by ortho-substituents in the phenylhydrazine. If the effect of the 4-substituent were solely steric, it would be expected that this critical stage would be the initial formation of the hydrazone (VI). This is not so, however, because we find that all our thioindoxyls react readily in the cold with 2 : 4-dinitrophenylhydrazine to give the corresponding 2 : 4-dinitrophenylhydrazones. The latter compounds, when derived from a 4-substituted thioindoxyl, therefore possess both types of substituents which inhibit the complete indolisation.

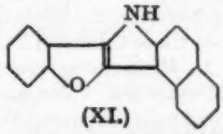
It is possible that the thioindoxyls always react in the enol form with hydrazines to give the hydrazides of type (VII) without intermediate formation of a true hydrazone of type (VI). This receives some support from the fact that 3-acetoxythionaphthens of type (IX) also react readily with phenylhydrazine to form thionaphthindoles (McClelland and D'Silva, *loc. cit.*). Furthermore, these authors state that 1 : 1-dioxythioindoxyl (X) gives a phenylhydrazone which cannot be indolised : they consider that the free valency electrons of the sulphone group



(IX.)



(X.)



(XI.)

decrease (or possibly entirely suppress) the enolisation of (X) which therefore forms a true hydrazone, which in turn cannot tautomerise to the hydrazide; hence the indolisation process is arrested. It is difficult, however, to adduce any steric or electronic reason why a 4-substituent in thioindoxyl should suppress enolisation: we have used only methyl, chloro- and 4 : 5-benz-groups; the effect of a 4-nitro-group, having an opposite and much stronger electronic influence than the methyl and chloro-group, would repay investigation.

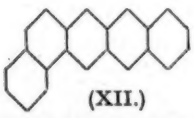
Parallel examples of the inhibiting effect of an ortho-substituent in the phenylhydrazine are known. Thus McClelland and Smith (*J.*, 1945, 408) have shown that although 3-hydroxy-2-acetylthionaphthen reacts readily with *m*- and *p*-nitrophenylhydrazine to give thionaphthenopyrazoles, the reaction with *o*-nitro- and 2 : 4-dinitro-phenylhydrazine goes no further than the formation of the corresponding nitrophenylhydrazones. Similarly Cawley and Plant (*J.*, 1938, 1216) have shown that although coumaranone reacted readily with β-naphthylhydrazine to form coumarono-(2′ : 3′ : 1 : 2)-β-naphthindole (XI), the reaction with both *o*- and *m*-nitrophenylhydrazines stopped at the nitrohydrazone stage. Finally Barclay and Campbell (*J.*, 1945, 530) found that *cyclo*hexanone *o*-tolylhydrazone decomposed rapidly even at room temperature without detectable conversion into a tetrahydrocarbazole: this was in striking contrast to the ready formation of the carbazole from the unsubstituted phenylhydrazone.

Since our work has shown that either a methyl or a nitro-group (groups opposite in their electronic effects) in the ortho-position in phenylhydrazine inhibits indolisation, it would appear that this result must be steric rather than electronic. Cawley and Plant's result with *m*-nitrophenylhydrazine is exceptional, and deserves fuller investigation.

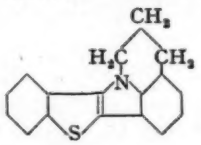
The reaction of thioindoxyl with *m*-tolylhydrazine can theoretically give rise to 1- or 3-*methylthionaphthindole*. It is possible that our product, although of sharp m. p. and apparently homogeneous, may be a mixture of these isomerides, for *cyclo*hexanone *m*-nitrophenylhydrazone on cyclisation gives a mixture (probably equimolecular) of 5- and 7-nitrotetrahydrocarbazoles which also has a sharp m. p. (Plant, *J.*, 1936, 899; Barclay and Campbell, *loc. cit.*).

It is known that if a polycyclic aromatic hydrocarbon possesses carcinogenic properties, a corresponding compound in which one of the aromatic rings has been replaced by a similar heterocyclic ring may also possess these properties. For example, the carcinogenic properties

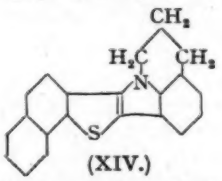
of 1 : 2 : 6 : 7-dibenzanthracene (XII) (Barry, Cook, *et al.*, *Proc. Roy. Soc.*, 1935, *B*, **117**, 318) appear also in 1 : 2 : 7 : 8-dibenzacridine. Carcinogenic properties are also shown by certain polycyclic sulphur compounds, such as 4 : 9-dimethyl-5 : 6-benzthiophanthrene (Sandin and Fieser, *J. Amer. Chem. Soc.*, 1940, **62**, 3098). There is an obvious similarity in general molecular outline between the dibenzanthracene (XII) and 11 : 12-benzthionaphthindole (IV). We have



(XII.)



(XIII.)



(XIV.)

consequently synthesised a number of these thionaphthindoles having additional rings, for therapeutic tests. In particular, the reaction of thioindoxyl with 1-amino-1 : 2 : 3 : 4-tetrahydroquinoline (mentioned above) readily furnished 4 : 6-*trimethylenethionaphthindole* (XIII), whereas the use of 6 : 7- and 5 : 6-benzthioindoxyls gave 4 : 6-*trimethylene*-11 : 12-*benzthionaphthindole* (XIV) and its 10 : 11-*benz*-isomeride. These three compounds represent new heterocyclic types. It is noteworthy that thionaphthindole (II) reacted readily with vinyl cyanide to form 6-(2-*cyanoethyl*)*thionaphthindole*, which on hydrolysis gave 6-(2-*carboxyethyl*)-*thionaphthindole*. Attempts to convert the latter into the corresponding acid chloride and then, by cyclisation with aluminium chloride, to obtain an independent synthesis of the ring system of (XIII) failed.

The thionaphthindoles all gave crystalline *picrates*, but it is noteworthy that the parent indole (II) and those of its derivatives having only four unsaturated rings all gave monopicrates, whereas those derivatives with five such rings all gave dipicrates. This further emphasises the resemblance between the thionaphthindoles and the polycyclic aromatic hydrocarbons.

Several of these thionaphthindoles containing additional fused rings are now being examined by Dr. A. L. Walpole in the Biological Laboratories of Imperial Chemical Industries Ltd., Blackley, Manchester. Preliminary tests indicate that certain of them may possess growth inhibitory action on experimental tumours; the results of carcinogenic tests are not yet available.

Towards certain reagents, the >NH group in thionaphthindole (II) and that in 11 : 12-benzthionaphthindole (IV) showed a striking difference in reactivity. This group in the parent indole (II), in addition to its ready combination with vinyl cyanide, could also be acetylated, whereas the same group in (IV) would undergo neither this cyanoethylation nor acetylation. This marked effect upon the reactivity of the >NH group by the remote extra ring is striking. Both compounds did, however, give N-*nitroso*-derivatives, which were too unstable even for recrystallisation.

The thioindoxyl 2 : 4-dinitrophenylhydrazones described above and tabulated later were all too insoluble for recrystallisation, and their isolation in the pure state was therefore dependent upon the use of pure thioindoxyls, free in particular from traces of the corresponding thioindigos which they form so readily by atmospheric oxidation. We have therefore purified the thioindoxyls by sublimation in a vacuum, after which they usually showed m. p.s markedly higher than previously recorded values.

We have been unable to effect indolisation by heating thio-oxindole with phenylhydrazine in acetic acid solution. Had indolisation occurred, a thionaphthindole isomeric with (II), but having the >S and >NH in the *cis*- instead of the *trans*-position, should have resulted.

Experimental.

The preparation of various thionaphthindoles from the thioindoxyls is described first, followed by the reactions of certain of these compounds. The properties of the pure thioindoxyls and of their 2 : 4-dinitrophenylhydrazones are tabulated subsequently.

The names of solvents used for recrystallisation are given in parenthesis after the compounds concerned.

Preparation of Thionaphthindoles.—1. *From thioindoxyl.* (i) Phenylhydrazine (11·2 c.c.) was added to a stirred solution of thioindoxyl (15 g.) in acetic acid (100 c.c.) at 40°; the temperature soon rose to 105° as the indole separated. The stirred mixture was maintained at 95—100° for 30 minutes. The thionaphthindole (II) was then collected from the cold mixture, washed with alcohol and water, and dried; 19·8 g.(89%).

It readily furnished a *monopicrate*, reddish-brown needles (alcohol), m. p. 171° (decomp.) (Found : N, 12·3. $C_{14}H_9NS,C_6H_3O_7N_3$ requires N, 12·4%); a *monostyphnate*, brick-red needles (alcohol), m. p. 175—176° (decomp.) (Found : N, 11·9. $C_{14}H_9NS,C_6H_3O_8N_3$ requires N, 11·9%); a *picrolonate*, yellow needles (alcohol), m. p. 188° (decomp.) (Found : N, 14·3. $C_{14}H_9NS,C_{10}H_8O_5N_4$ requires N, 14·4%).

(ii) Solutions of *p*-nitrophenylhydrazine (2·9 g.) and thioindoxyl (2·8 g.), each in acetic acid (20 c.c.), were mixed, whereupon a red product, presumably the hydrazone, immediately separated, but subsequently redissolved with deposition of the indole, when the mixture was heated at 100° for 30 minutes. The *2-nitrothionaphthindole* when collected and recrystallised (xylene) formed yellow needles: owing to their low solubility they were further purified by sublimation at 0·1 mm. (jacket temperature, 260°); m. p. 350—352° (decomp.) (Found: C, 62·5; H, 2·9; N, 10·7. $C_{14}H_8O_2N_2S$ requires C, 62·7; H, 3·0; N, 10·5%).

(iii) *m*-Tolylhydrazine similarly gave 1 (or 3)-*methylthionaphthindole*, colourless leaflets (alcohol), m. p. 256° (Found: C, 76·4; H, 4·9. $C_{15}H_{11}NS$ requires C, 76·0; H, 4·6%); the *monopicrate* formed brown crystals, m. p. 185° (decomp.) (Found: N, 12·1. $C_{15}H_{11}NS,C_6H_3O_7N_3$ requires N, 12·0%).

(iv) 1-Amino-1 : 2 : 3 : 4-tetrahydroquinoline was prepared by Holliman and Mann's method (*J.*, 1942, 737). A solution of the sulphate (4 g.) in acetic acid (40 c.c.) and one of thioindoxyl (3 g.) and anhydrous sodium acetate (2 g.), also in acetic acid (40 c.c.), were mixed and refluxed for 30 minutes. When cold, the *4 : 6-trimethylenethionaphthindole* (XIII) [3·3 g. (63%)] was collected, washed with alcohol and hot water, and recrystallised (alcohol); colourless leaflets, m. p. 139° (Found: C, 77·2; H, 5·6; N, 5·1. $C_{17}H_{13}NS$ requires C, 77·6; H, 4·9; N, 5·3%). It gave a *monopicrate*, bluish-black needles (alcohol), m. p. 149° (Found: N, 11·7. $C_{17}H_{13}NS,C_6H_3O_7N_3$ requires N, 11·4%).

2. *From 5-chloro-7-methylthioindoxyl.* (i) *p*-Tolylhydrazine hydrochloride, with sodium acetate and the thioindoxyl, readily gave *10-chloro-2 : 12-dimethylthionaphthindole*, pale-brown crystals (alcohol) m. p. 241° (Found: C, 67·5; H, 4·5. $C_{16}H_{12}NClS$ requires C, 67·3; H, 4·2%); the *monopicrate* formed deep bronze leaflets (alcohol containing picric acid), m. p. 201° (decomp.) (Found: N, 11·1. $C_{16}H_{12}NClS,C_6H_3O_7N_3$ requires N, 10·9%).

(ii) 1-Phenyl-2-ethylhydrazine and the thioindoxyl, refluxed together in acetic acid solution, readily gave *10-chloro-12-methyl-6-ethylthionaphthindole*, pale purple leaflets (alcohol), m. p. 165° (Found: C, 68·0; H, 4·8; N, 4·7. $C_{17}H_{14}NClS$ requires C, 68·1; H, 4·7; N, 4·7%); the *monopicrate* formed ruby-red needles, m. p. 129° (Found: N, 11·5. $C_{17}H_{14}NClS,C_6H_3O_7N_3$ requires N, 11·3%).

Both the above indoles were considerably more soluble in alcohol than most of the other indoles isolated in this investigation.

3. *From 6-ethoxythioindoxyl.* Phenylhydrazine gave *11-ethoxythionaphthindole*, white needles (alcohol), m. p. 243° (Found: C, 72·3; H, 5·2. $C_{16}H_{13}ONS$ requires C, 71·9; H, 4·9%).

4. *From 6 : 7-benzthioindoxyl.* (i) Phenylhydrazine gave *11 : 12-benzthionaphthindole* (IV), white crystals (alcohol), m. p. 325—326° (Found: C, 79·3; H, 4·3. $C_{18}H_{11}NS$ requires C, 79·1; H, 4·0%); the *dipicrate* formed bronze-coloured leaflets (alcohol containing picric acid), m. p. 178—180° (decomp.) (Found: N, 13·4. $C_{18}H_{11}NS,2C_6H_3O_7N_3$ requires N, 13·4%). The indole was unaffected by 1 hour's refluxing with acetic anhydride.

(ii) *p*-Nitrophenylhydrazine by the usual treatment and isolation gave *2-nitro-11 : 12-benzthionaphthindole*, purified by vacuum sublimation, orange-brown crystals, m. p. 380—382° (Found: C, 67·7; H, 3·0; N, 8·8. $C_{18}H_{10}O_2N_2S$ requires C, 67·9; H, 3·1; N, 8·8%).

(iii) *p*-Tolylhydrazine gave *2-methyl-11 : 12-benthionaphthindole*, colourless crystals (alcohol), m. p. 318° (Found: C, 79·6; H, 4·8. $C_{19}H_{13}NS$ requires C, 79·4; H, 4·5%); the *dipicrate* formed purple-brown needles, m. p. 186—187° (decomp.) (Found: N, 13·1. $C_{19}H_{13}NS,2C_6H_3O_7N_3$ requires N, 13·1%).

(iv) 1-Phenyl-2-methylhydrazine gave *6-methyl-11 : 12-benzthionaphthindole*, silvery plates (alcohol), m. p. 226° (Found: C, 79·5; H, 4·6. $C_{19}H_{13}NS$ requires C, 79·4; H, 4·5%); the *dipicrate* formed deep brown needles (alcohol), m. p. 165° (Found: N, 12·9. $C_{19}H_{13}NS,2C_6H_3O_7N_3$ requires N, 13·1%).

(v) 1-Amino-1 : 2 : 3 : 4-tetrahydroquinoline gave *4 : 6-trimethylene-11 : 12-benzthionaphthindole* (XIV), silvery crystals by vacuum sublimation, m. p. 237° (Found: C, 80·4; H, 5·2; N, 4·6. $C_{21}H_{15}NS$ requires C, 80·5; H, 4·8; N, 4·5%); the *dipicrate* formed chocolate needles (toluene), m. p. 184° (Found: N, 12·6. $C_{21}H_{15}NS,2C_6H_3O_7N_3$ requires N, 12·7%).

5. *From 5 : 6-benzthioindoxyl.* (i) Phenylhydrazine gave *10 : 11-benzthionaphthindole*, (V), very pale green plates (toluene), m. p. 358° (Found: C, 79·0; H, 4·3; N, 4·9. $C_{18}H_{11}NS$ requires C, 79·1; H, 4·0; N, 5·1%).

(ii) 1-Amino-1 : 2 : 3 : 4-tetrahydroquinoline gave *4 : 6-trimethylene-10 : 11-benzthionaphthindole*, pale yellow needles by vacuum sublimation, m. p. 195—197° (Found: C, 80·8; H, 4·4. $C_{21}H_{15}NS$ requires C, 80·5; H, 4·8%).

6. *From 5-methylthioindoxyl.* (i) *p*-Tolylhydrazine gave *2 : 10-dimethylthionaphthindole*, pale brown needles (alcohol), m. p. 304° (Found: C, 76·6; H, 5·6. $C_{16}H_{13}NS$ requires C, 76·5; H, 5·2%).

7. *From 7-methylthioindoxyl.* (i) Phenylhydrazine gave *12-methylthionaphthindole*, colourless leaflets (alcohol), m. p. 202° (Found: C, 76·3; H, 4·8. $C_{15}H_{11}NS$ requires C, 76·0; H, 4·6%); the *monopicrate* formed deep brown needles (alcohol), m. p. 186—188° (decomp.) (Found: N, 12·2. $C_{15}H_{11}NS,C_6H_3O_7N_3$ requires N, 12·0%).

8. *From 7-chlorothioindoxyl.* (i) Phenylhydrazine gave *12-chlorothionaphthindole*, colourless leaflets (acetic acid, then alcohol), m. p. 223° (Found: C, 65·4; H, 3·0. $C_{14}H_8NCIS$ requires C, 65·3; H, 3·1%); the *monopicrate* formed reddish-bronze needles (alcohol containing picric acid), m. p. 178° (decomp.) (Found: N, 11·5. $C_{14}H_8NCIS,C_6H_3O_7N_3$ requires N, 11·5%).

Reactions of Thionaphthindole.—(1) *Formylation.* A mixture of the indole (2 g.), formic acid (98—100%, 40 c.c.), and acetic anhydride (10 c.c.) was refluxed for 2·5 hours, cooled, and poured into water. The precipitated material when crystallised (alcohol) furnished colourless needles of *6-formylthionaphthindole*, m. p. 145° (Found: C, 71·9; H, 3·9. $C_{15}H_9ONS$ requires C, 71·7; H, 3·6%); the *picrate* formed brown needles (alcohol), m. p. 148—150° (decomp.) (Found: N, 11·8. $C_{15}H_9ONS,C_6H_3O_7N_3$ requires N, 11·7%).

(2) *Nitrosation.* An aqueous solution of sodium nitrite (1·5 g.) was added slowly with stirring to a solution of the indole (1·5 g.) in cold acetic acid (350 c.c.). The precipitated yellow needles of the *6-nitrosothionaphthindole* were collected, washed with alcohol and water, and dried; m. p. 151—153° (decomp.) (Found: C, 67·1; H, 3·1; N, 11·0. $C_{14}H_{10}ON_2S$ requires C, 66·7; H, 3·2; N, 11·1%). Attempted recrystallisation of this compound from alcohol regenerated the indole.

(3) *Cyanoethylation.* A mixture of the indole (1·5 g.), vinyl cyanide (10 c.c.), dioxan (10 c.c.), and a trace of sodium methoxide was refluxed for 1·5 hours, and then poured into water (400 c.c.). The precipitate when recrystallised (alcohol) furnished 6-(2-*cyanoethyl*)*thionaphthindole*, pale yellow crystals, m. p. 167° (Found: C, 73·7; H, 4·7; N, 10·1. $C_{17}H_{12}N_2S$ requires C, 73·9; H, 4·5; N, 10·1%); 1·6 g. (86%).

For hydrolysis, a mixture of the cyanide (2·76 g.), potassium hydroxide (2 g.), alcohol (65 c.c.), and water (10 c.c.) was refluxed for 3·5 hours. The cyanide dissolved during the first 15 minutes' boiling, and the clear solution then deposited colourless crystals which subsequently redissolved. The final solution was poured into water (400 c.c.), and next day the small precipitate was removed, and the filtrate acidified with hydrochloric acid. The precipitated 6-(2-*carboxyethyl*)*thionaphthindole* [2·45 g. (83%)] gave colourless needles (50% aqueous alcohol), m. p. 168° (Found: C, 69·2; H, 4·7. $C_{17}H_{13}O_2NS$ requires C, 69·2; H, 4·4%). It is essential that the pure cyanide is used for this hydrolysis.

For attempted cyclisation, thionyl chloride (1·3 c.c., 1·5 mols.) was added to the above acid (3·6 g.) in dry benzene (35 c.c.) and the mixture refluxed until hydrogen chloride evolution ceased (*ca.* 1 hour). Powdered aluminium chloride (3 g.) was then added, and the refluxing continued for 3 hours more; considerable tar was produced. After addition of water, the benzene was removed in steam, and the dried residue then extracted (Soxhlet) with light petroleum (b. p. 60—80°). Evaporation of the extract gave only a minute residue.

Reactions of 11 : 12-*Benzthionaphthindole.*—(1) *Nitrosation.* This process, performed as in (2) above, furnished 6-*nitroso*-11 : 12-*benzthionaphthindole*, yellow needles, m. p. 164—165° (decomp.) (Found: N, 8·9. $C_{18}H_{10}ON_2S$ requires N, 9·2%). The compound decomposed on attempted recrystallisation.

(2) *Attempted cyanoethylation.* When a mixture of the indole (1·3 g.), vinyl cyanide (5 c.c.), dioxan (8 c.c.), and a trace of sodium methoxide was refluxed for 1·5 hours, and the solvents were then removed under reduced pressure, recrystallisation of the residue afforded only unchanged indole.

Formation of the Thioindoxyl 2 : 4-*Dinitrophenylhydrazones.*—Since these *compounds* could not be recrystallised without decomposition, they were prepared from purified thioindoxyls. For this purpose, thioindoxyl was distilled in steam, but the substituted thioindoxyls were sublimed at *ca.* 0·2 mm., jacket-temperature approximating to m. p. of the thioindoxyl. For the hydrazone formation, an alcoholic solution of 2 : 4-dinitrophenylhydrazine hydrochloride was added to a cold alcoholic solution of the pure thioindoxyl: the hydrazone rapidly separated, and was ultimately collected, washed with alcohol and ether, and dried. The properties of the thioindoxyls and their hydrazones are given in the following Table.

Thio-indoxyl.	Properties of purified thioindoxyl.	Properties of 2 : 4-dinitro-phenylhydrazones.	Formula.	Nitrogen (%). Found.	Required.
Unsubst.		Scarlet, m. p. 230° with darkening above 175°.	$C_{14}H_{10}O_4N_4S$	17·0	17·0
6-Cl-4-Me	Pale yellow needles, m. p. 106—108°.	Brick red, m. p. 217—218°.	$C_{15}H_{11}O_4N_4ClS$	14·6	14·8
5-Cl-7-Me	Cream crystals, m. p. 102—103°.	Scarlet, m. p. 216—218°, darkening above 195°.	$C_{15}H_{11}O_4N_4ClS$	14·9	14·8
6-EtO	Pale yellow crystals, m. p. 123—124°.	Scarlet, m. p. 217—219°, darkening above 185°.	$C_{16}H_{14}O_5N_4S$	15·2	15·0
4 : 5-Benz	Yellow crystals, m. p. 122—123°.	Scarlet, m. p. 199—200°.	$C_{18}H_{12}O_4N_4S$	14·8	14·7
6 : 7-Benz	Orange crystals, m. p. 142—143°.	Scarlet, m. p. 235—237°, darkening above 200°	$C_{18}H_{12}O_4N_4S$	15·0	14·7
4-Cl	Yellow needles, m. p. 113—114°.	Orange, m. p. 205°.	$C_{14}H_9O_4N_4ClS$	15·4	15·4
4 : 7-Dichloro	Yellow crystals, m. p. 140—141°.	Orange, m. p. 210°.	$C_{14}H_8O_4N_4Cl_2S$	14·3	14·0
5-Me	(Not sublimed)	Deep red, m. p. 227—228°, darkening above 190°.	$C_{15}H_{12}O_4N_4S$	16·6	16·3
7-Cl	Pale orange needles, m. p. 136—140°.	Orange, m. p. 242—243°.	$C_{14}H_9O_4N_4ClS$	15·6	15·4

All the above hydrazones are new, all melt with decomp., and all are microcrystalline.

We are indebted to Imperial Chemical Industries Ltd. (Dyestuffs Division) for materials.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 17th,* 1946.]

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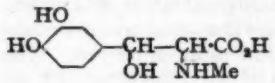
125. *The Synthesis of* β-(3 : 4-*Dihydroxyphenyl*)-N-*methylserine* (*Adrenalinecarboxylic Acid*).

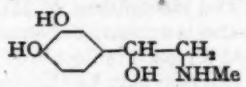
By CHARLES E. DALGLIESH and FREDERICK G. MANN.

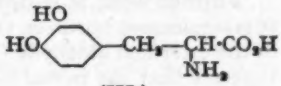
The above amino-acid has been synthesised by the interaction of 3 : 4-diethylcarbonatobenzaldehyde and sarcosine ethyl ester in the presence of sodium. A possible mechanism of the reaction is suggested, and a number of intermediate derivatives are described.

β-(3 : 4-*Dihydroxyphenyl*)-N-*methylserine* (I) is a compound of considerable pharmacological interest in view of its intermediate relationship to adrenaline (II) and "dopa" (III), and we have consequently investigated its synthesis.

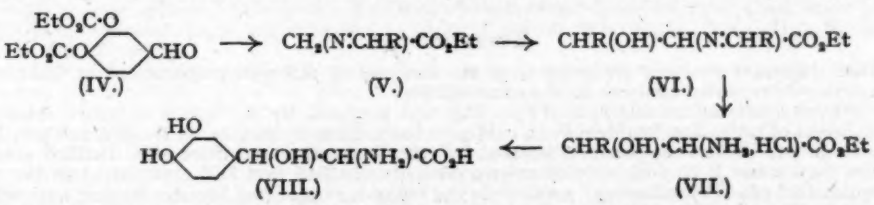
Erlenmeyer (*Annalen*, 1895, **284**, 36) has shown that when certain aromatic aldehydes, for example benzaldehyde, react with glycine in aqueous sodium hydroxide solution, a Schiff's base of type $CH_2(N{:}CHPh)\cdot CO_2H$ is first formed and then undergoes an aldol condensation with a second molecule of aldehyde to give compounds of type $CHPh(OH)\cdot CH(N{:}CHPh)\cdot CO_2H$; hydrolysis then furnishes the α-amino-β-hydroxy-acid $CHPh(OH)\cdot CH(NH_2)\cdot CO_2H$. This condensation is markedly affected by substituents in the phenyl group; Erlenmeyer and Bade


(I.)


(II.)


(III.)

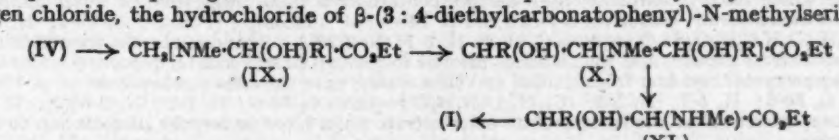
(*ibid.*, 1904, **337**, 235) showed that, although the methyl ether of salicylaldehyde readily underwent the above series of reactions, *p*-anisaldehyde failed to do so. Even when methoxyphenyl derivatives can be obtained by this method, demethylation without dehydration or deamination would be difficult (cf. Barger and Jowett, *J.*, 1905, **87**, 967). To prepare hydroxyphenyl analogues, Rosenmund and Dornsaft (*Ber.*, 1919, **52**, 1734) therefore converted protocatechualdehyde into the dicarbethoxy-derivative (IV), which was treated in ethereal solution with glycine ethyl ester and sodium. They adduced evidence that in this reaction also the initial reaction was the formation of the Schiff's base (V, R = 3 : 4-diethylcarbonatophenyl), which


(IV.) (V.) (VI.) (VII.) (VIII.)

then underwent a similar aldol condensation to (VI). By hydrolysis with alcoholic hydrogen chloride they isolated the crystalline β-(3 : 4-diethylcarbonatophenyl)serine ethyl ester hydrochloride (VII), which after alkaline hydrolysis in a hydrogen atmosphere yielded β-(3 : 4-dihydroxyphenyl)serine (VIII).

We have repeated this synthesis in the hope that *N*-methylation of (VII) would be practicable. (VII) was treated in absolute alcoholic solution first with one equivalent of sodium ethoxide to liberate the free amine and then with diazomethane: no methylation occurred, however, and the amine was ultimately recovered unchanged. (VII) was also treated with benzenesulphonyl chloride in various solvents in the hope that the sulphonamido-compound could subsequently be methylated and the benzenesulphonyl groups then removed catalytically: the benzenesulphonyl derivative formed a glass, however, and could not be purified. It is noteworthy that Rosenmund and Dornsaft's reaction is also critically affected by the nature of the substituents in the benzene ring; we have been unable to condense glycine ester with either veratraldehyde or piperonal under the above conditions.

We have consequently investigated the condensation of various aldehydes in ethereal solution with sarcosine ethyl ester in the presence of sodium, although the absence of a primary amino-group in sarcosine would prevent a series of reactions strictly analogous to those adduced by Rosenmund and Dornsaft. In earlier experiments we could not detect any reaction between veratraldehyde and sarcosine ester or nitrile under these conditions. 3 : 4-Diethylcarbonatobenzaldehyde did, however, react with sarcosine ester in the presence of sodium, the reaction at room temperature requiring about 36 hours. When the product was hydrolysed with alcoholic hydrogen chloride, the hydrochloride of β-(3 : 4-diethylcarbonatophenyl)-N-methylserine ethyl


(IV) (IX.) (X.) (I) (XI.)

ester (XI, R as before) was isolated as a gum which could not be crystallised. It gave a crystalline *picrate*, and when treated in aqueous solution with potassium oxalate gave a crystalline

monohydrated *oxalate*. Recrystallisation of the crude oxalate gave the highly crystalline monohydrated *hydrogen oxalate*, the yield of which, based on the esterified aldehyde and allowing for recovered aldehyde, was 6%.

Alkaline hydrolysis of the hydrogen oxalate in an atmosphere of hydrogen (cf. Rosenmund and Dornsaft), using either sodium or barium hydroxide, failed to give the pure acid. Hydrolysis with dilute acetic acid in an inert atmosphere, however, funished the required β-(3 : 4-dihydroxyphenyl)-*N*-methylserine (I), as cream-coloured crystals, m. p. 233° (decomp.), the yield of the recrystallised acid being 65% based on the hydrogen oxalate used, and 3·9% based on (IV) and allowing for recovered aldehyde.

Further work is required before the mechanism of the above condensation is elucidated. It is significant, however, that the synthesis appears to be successful only if at least two molecules of the esterified aldehyde (IV) are used for each molecule of the sarcosine ester employed. This suggests that the initial stage in the reaction may be the combination of sarcosine ester with one molecule of the aldehyde to give a compound of type (IX), which then unites with a second molecule to give the compound (X); finally the hydrolysis with alcoholic hydrogen chloride removes the first molecule of the aldehyde, giving the esterified amino-acid (XI).

It is noteworthy that throughout our synthesis no indication was obtained of the existence of more than one racemate, and it is at present impossible to say whether our amino-acid has the same configuration as that of naturally occurring adrenaline. In the synthesis of compounds such as $CHPh(OH)\cdot CHPh\cdot NH_2$, different racemates are obtained according to the method employed (cf. Dodds, Lawson and Williams, *Nature*, 1944, **154**, 514; *Proc. Roy. Soc.*, 1944, *B*, **132**, 119; McPhee and Erickson, *J. Amer. Chem. Soc.*, 1946, **68**, 621).

Experimental.

When duplicate analyses are given they are analyses of different preparations of the compound, and not merely repeated analyses on the same sample.

3 : 4-*Diethylcarbonatobenzaldehyde* (IV).—This was prepared by the action of ethyl chloroformate on a solution of protocatechualdehyde in cold aqueous sodium hydroxide, as Rosenmund and Dornsaft (*loc. cit.*) direct. When the product, isolated by ether extraction and dried, was distilled even at low pressure (<0·1 mm.), 3 : 4-carbonyldioxybenzaldehyde distilled first and crystallised in the receiver, the liquid aldehyde (IV) following; meanwhile the liquid-air trap often became blocked with solid ethyl carbonate. To reduce this decomposition of the aldehyde (IV) to a minimum it was distilled rapidly in moderate quantities, using a high-capacity pump with large traps to avoid choking. The distillation could then be continued without interruption, and the required product, b. p. 186°/0·03 mm., 193°/0·1 mm., (65% yield), could ultimately be either obtained as a separate fraction or, if decomposition was unusually extensive, decanted from the carbonyl-aldehyde which had crystallised in the receiver. It was characterised as the 2 : 4-*dinitrophenylhydrazone*, orange crystals from ethyl acetate, m. p. 165° (Found: N, 12·6. $C_{19}H_{16}O_{10}N_4$ requires N, 12·2%). The aldehyde (IV), after recrystallisation from benzene, had m. p. 122°.

Derivatives of β-3 : 4-*Dihydroxyphenylserine* (VIII).—The aldehyde (IV) (67·5 g.), freshly prepared glycine ethyl ester (12·5 g.), and sodium wire (5·5 g.) in ether (200 c.c.) were shaken vigorously together at intervals over a period of 36 hours (cf. Rosenmund and Dornsaft, *loc. cit.*). Alcoholic hydrogen chloride was added to the filtered solution whereupon the hydrochloride (VII) was deposited as an oil. This was twice extracted with water, and the aqueous extract again extracted with ether. A portion of the aqueous extract was treated with sodium picrate, giving β-(3 : 4-*diethylcarbonatophenyl*)*serine ethyl ester picrate*, yellow needles from alcohol, m. p. 152° (Found: N, 9·3. $C_{15}H_{22}O_9N,C_6H_3O_7N_3$ requires N, 9·5%). The remainder of the extract was evaporated in a vacuum, and the residue, crystallised from alcohol, gave colourless needles of the corresponding hydrochloride (VII), m. p. 152—153°; 14·2 g. [14% based on the aldehyde (IV)].

Alkaline hydrolysis of (VII) gave β-(3 : 4-dihydroxyphenyl)serine (VIII), colourless crystals from water, m. p. 219—221° (Found: N, 6·4. Calc. for $C_9H_{11}O_5N$: N, 6·5%); yield, 28% based on the hydrochloride (VII). Rosenmund and Dornsaft (*loc. cit.*) give m. p. 208—210°. The acid gives a *picrate*, orange crystals, m. p. 90—92° (Found: N, 12·5. $C_9H_{11}O_5N,C_6H_3O_7N_3$ requires N, 12·6%); it also gives a marked and ready ninhydrin reaction on warming.

It is probable that the acid hydrolysis subsequently devised for the *N*-methyl compound (XI), if applied to (VII), would give considerably greater yields of the amino-acid (VIII).

The hydrochloride (VII) when treated in aqueous solution with potassium oxalate gave a sticky precipitate which on crystallisation from alcohol containing a small proportion of water afforded the *ester oxalate monohydrate*, colourless crystals, m. p. 140—141° (decomp.) (Found: C, 49·4; H, 6·0; N, 3·6. $2C_{17}H_{23}O_9N,C_2H_2O_4,H_2O$ requires C, 49·2; H, 5·7; N, 3·2%). This oxalate was treated in aqueous solution with silver nitrate, and the solution, filtered to remove silver oxalate, deposited white leaflets: these, when recrystallised first from alcohol and then water, gave the *ester monohydrate*, m. p. 138—139° (Found: C, 50·6; H, 5·7; N, 3·5. $C_{17}H_{23}O_9N,H_2O$ requires C, 50·6; H, 6·2; N, 3·5%). It is clear from this experiment that the intermediate ester nitrate must have undergone dissociation to liberate the free ester.

Attempted Methylation.—Sodium ethoxide solution (sodium, 0·23 g.: alcohol, 5 c.c.) was added to a solution of the hydrochloride (VII) (4·2 g.) in alcohol (15 c.c.). The mixture was rapidly filtered and treated with an ethereal solution of diazomethane [30 c.c., 0·5 g. CH_2N_2 (1·2 mols.)]. The solution was

subsequently treated with alcoholic hydrogen chloride, but ultimately only the unchanged ester (as VII), isolated as its picrate, could be identified.

When ethereal solutions of 3 : 4-carbonyldioxybenzaldehyde and glycine ester were mixed in the absence of sodium, a turbidity rapidly developed and a yellow oil was deposited. In the absence of ether, the two compounds reacted vigorously with much heat evolution, and the orange-coloured resin formed a glass which could not be purified.

Sarcosine Nitrile and Ethyl Ester.—Staudt's method (*Z. physiol. Chem.*, 1925, **146**, 286) for the preparation of sarcosine nitrile was found to be most effective, carbon dioxide being passed through a stirred, cooled aqueous solution of methylamine sulphate, formaldehyde, and potassium cyanide. Contrary to published statements, the nitrile could be distilled with very little decomposition as a colourless viscous liquid, b. p. 95—105°/0·2 mm., which remained unchanged after several months. Yield, 68% based on the methylamine. It gave a *picrate*, yellow needles from alcohol, m. p. 142—143° (Found : N, 23·4. $C_3H_6N_2,C_6H_3O_7N_3$ requires N, 23·4%). The nitrile was converted into the ester hydrochloride by Staudt's method (*loc. cit.*), and the free ester isolated by treating the hydrochloride in ice-cold aqueous solution with 30% sodium hydroxide solution, followed by rapid ether extraction and distillation; colourless liquid, b. p. 52°/15 mm.; yield, 37% based on the nitrile, 25% on the methylamine employed.

Derivatives of β-(3 : 4-Dihydroxyphenyl)-N-methylserine (I).—Fine sodium wire (7 g., 7 atoms) was added to a mixture of the aldehyde (IV) (90 g., 2 mols.) and freshly distilled sarcosine ethyl ester (17·3 g., 1 mol.) in dry ether (450 c.c.); glass beads or fragments of porcelain were also added. Effervescence occurred, and the sodium became covered with a yellow film. The mixture was vigorously shaken at intervals, the beads assisting the removal of this film from the sodium. No detectable reaction had occurred after 12 hours, but the occasional shaking was continued for 36 hours; a shorter period caused a decreased yield. Ether was then added until deposition of a yellow material (in small amount) ceased, and alcoholic hydrogen chloride was then added to the filtered solution until precipitation of the crude hydrochloride of the ester (XI) was complete. This yellow viscous hydrochloride was twice extracted with water, and the extract, after being shaken with ether, was evaporated under reduced pressure, depositing the hydrochloride as an uncrystallisable gum. A portion of this gum, dissolved in water and treated with sodium picrate, gave *β-(3 : 4-diethylcarbonatophenyl)-N-methylserine ethyl ester picrate*, yellow plates from alcohol, m. p. 144° (Found : C, 46·3; H, 4·8; N, 9·1. $C_{18}H_{25}O_9N,C_6H_3O_7N_3$ requires C, 45·9; H, 4·5; N, 8·9%).

Aqueous potassium oxalate solution was added to a concentrated solution of the gummy hydrochloride, precipitating an oil which crystallised after the mixture had been set aside overnight. This crude oxalate was collected, and the filtrate then slowly deposited white crystals of the pure *oxalate monohydrate* of the above ester (XI), m. p. 147° (decomp.) (Found : C, 50·5; H, 5·9; N, 3·2. $2C_{18}H_{25}O_9N,C_2H_2O_4,H_2O$ requires C, 50·3; H, 5·9; N, 3·1%). The crude oxalate, when recrystallised from alcohol containing a small proportion of water, afforded the *hydrogen oxalate monohydrate*, glistening white leaflets, m. p. 157° (decomp.) (Found : C, 47·5, 47·5; H, 5·8, 5·7; N, 3·0, 2·9. $C_{18}H_{25}O_9N,C_2H_2O_4,H_2O$ requires C, 47·3; H, 5·7; N, 2·8%); yield, 3·2 g. (2% based on initial esterified aldehyde, 6% allowing for recovered aldehyde). This oxalate was unchanged when heated at 80°/0·1 mm. (Found : C, 47·5; H, 5·6%); m. p. 157° (decomp.). It is probable that the crude oxalate initially precipitated consisted mainly of the hydrogen oxalate. Had it consisted of the normal oxalate, recrystallisation must have involved dissociation to the hydrogen oxalate and the free base; yet the mother-liquor from the recrystallisation, when treated with oxalic acid, gave no further precipitation of the hydrogen oxalate, although with picric acid it furnished the above picrate.

A portion of the hydrogen oxalate in aqueous solution was treated with silver nitrate (2 mols.), as in the experiment with the unmethylated product, but neither the ester nitrate nor the free ester could be isolated.

The ethereal residues from the preparation of the crude hydrochloride were united, dried, and distilled. After removal of the ether, an unidentified fraction, b. p. 110—130°/0·2 mm., was obtained, but the residual esterified aldehyde (60 g.) could not be distilled without decomposition. It was therefore hydrolysed by refluxing with 5% hydrochloric acid (charcoal) for 3 hours, and the filtered solution was then evaporated under reduced pressure until crystallisation of protocatechualdehyde began; the mixture was cooled and the aldehyde collected, dried, and re-esterified for subsequent preparations.

Hydrolysis. A solution of the pure hydrogen oxalate monohydrate (2·3 g.) in acetic acid (30 c.c.) and water (70 c.c.) was refluxed in nitrogen atmosphere for 6 hours. The solution was concentrated under reduced pressure, and then taken to dryness in a vacuum desiccator. The residue, crystallised from water containing a small proportion of alcohol, gave cream-coloured crystals of *β-(3 : 4-dihydroxyphenyl)-N-methylserine* (I), m. p. 233° (decomp., with darkening above 220°) (Found : C, 53·1; 53·1; H, 5·4, 5·5; N, 6·1. $C_{12}H_{15}O_5N$ requires C, 52·9; H, 5·7; N, 6·2%). Yield of recrystallised acid, 0·65 g. [65% based on oxalate, 3·5% based on (IV) allowing for recovered aldehyde].

Alternatively, the crude unrecrystallised oxalate was hydrolysed as above, and the solution then concentrated under reduced pressure, cooled, and diluted with acetone. The acid (I) was deposited as colourless needles, m. p. 233° (decomp.), which, however, darkened slightly on recrystallisation. This method is quicker and the yield rather higher (1·3% based on initial esterified aldehyde, 3·9% allowing for recovered aldehyde).

Attempted alkaline hydrolysis of the oxalate with sodium hydroxide caused much oxidation, and with barium hydroxide gave a brown product from which total removal of the barium was difficult. Attempts to hydrolyse the crude hydrochloride directly, by boiling it, either alone in aqueous solution or with dilute acetic acid containing sodium acetate, did not prove satisfactory.

The amino-acid (I) is moderately soluble in cold water, and oxidises readily in aqueous solution, especially in the presence of alkalis. It is almost insoluble in cold, but slightly soluble in hot, alcohol. Its aqueous solution does not precipitate a picrate with picric acid solution. It gives a ninhydrin reaction, the aqueous solution on boiling becoming first red and then blue; this reaction occurs more slowly than with the unmethylated acid (VIII).

Attempts to condense veratraldehyde with sarcosine ester (*a*) in ether in the presence of sodium, (*b*) in a mixture of pyridine and acetic anhydride, (*c*) in a mixture of pyridine and piperidine (cf. Boyd and Robson, *Biochem. J.*, 1935, **29**, 542) all failed. Similarly, veratraldehyde could not be condensed with sarcosine nitrile in the presence of sodium.

We are greatly indebted to Imperial Chemical Industries Ltd., for materials.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 19th*, 1946.]

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126. *The Preparation and Properties of 2-Substituted* iso*Arsindolines and of* As-spiro-*Bis*iso*arsindolinium Salts.*

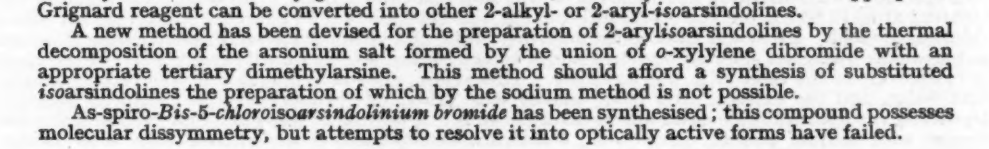
By DONALD R. LYON, FREDERICK G. MANN, and (in part) GERALD H. COOKSON.

A number of 2-aryl*iso*arsindolines (I) have been prepared by the action of *o*-xylylene dibromide and sodium on the corresponding aryldichloroarsines. Oxidation derivatives of these compounds proved, however, to have no greater activity against *T. congolense* in mice than those of the 2-phenyl member previously described. These 2-aryl*iso*arsindolines when heated with hydriodic acid readily give 2-*iodoisoarsindoline*, which by the action of the appropriate Grignard reagent can be converted into other 2-alkyl- or 2-aryl-*iso*arsindolines.

A new method has been devised for the preparation of 2-aryl*iso*arsindolines by the thermal decomposition of the arsonium salt formed by the union of *o*-xylylene dibromide with an appropriate tertiary dimethylarsine. This method should afford a synthesis of substituted *iso*arsindolines the preparation of which by the sodium method is not possible.

As-spiro-*Bis*-5-*chloro*iso*arsindolinium bromide* has been synthesised; this compound possesses molecular dissymmetry, but attempts to resolve it into optically active forms have failed.

IT has been shown by Lyon and Mann (*J.*, 1945, 30) that *o*-xylylene dibromide in ethereal solution reacts with phenyl- and methyl-dichloroarsine in the presence of sodium to form 2-phenyl*iso*arsindoline (I; R = Ph) and 2-methyl*iso*arsindoline (I; R = Me) respectively. These compounds possessed two particular points of interest. The phenyl compound when treated with nitric acid was readily oxidised to the corresponding hydroxynitrate (II; R = Ph, X = NO_3), which with alkali gave the dihydroxide (II; R = Ph, X = OH), and the latter on dehydration formed 2-phenyl*iso*arsindoline oxide (III; R = Ph). The preliminary tests showed that the dihydroxide possessed slight activity against *Trypanosoma rhodesiense*, *T. cruzi*, and *T. congolense* in mice. Secondly, the methylarsine (I; R = Me) readily combined



with a further molecule of *o*-xylylene dibromide, and the arsonium salt thus produced lost methyl bromide on heating with the formation of *As-spiro*-bis*iso*arsindolinium bromide (IV). This constituted the first synthesis of a spirocylic arsonium salt having the arsenic atom covalently joined to four carbon atoms. We have consequently investigated in greater detail both these aspects of the *iso*arsindolines.

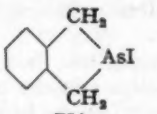
We have first prepared analogues of (I) containing aryl groups other than phenyl in the 2-position in order to determine whether the therapeutic action could thus be increased. *o*-Xylylene dibromide reacted readily with *p*-tolyldichloroarsine and sodium to form 2-p-*tolyl*iso*arsindoline* (I; R = *p*-C_6H_4Me); this compound resembled its phenyl analogue in that even after distillation it remained contaminated with cyclic hydrocarbons (cf. Lyon and Mann, *loc. cit.*). It was therefore converted into its *hydroxynitrate* (II; R = *p*-C_6H_4Me, X = NO_3) which was then purified by recrystallisation, converted into the *dihydroxide* (II; R = *p*-C_6H_4Me, X = OH), and the latter then reduced to the pure liquid arsine.

p-Chlorophenyldichloroarsine similarly furnished 2-p-*chlorophenyl*iso*arsindoline* (I; R = *p*-C_6H_4Cl); this arsine, initially liquid, had also to be purified *via* the *hydroxynitrate* (II; R = *p*-C_6H_4Cl, X = NO_3) and the *dihydroxide* (II; R = *p*-C_6H_4Cl, X = OH) and was thus obtained as colourless crystals, m. p. 64°.

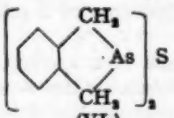
p-Anisyldichloroarsine furnished 2-p-*anisyl*iso*arsindoline* (I; R = *p*-C_6H_4·OMe), which readily solidified after an initial distillation, and was purified by direct crystallisation without the necessity for the intermediate formation of the *hydroxynitrate* (II; R = *p*-C_6H_4·OMe, X = NO_3) and the *oxide* (III; R = *p*-C_6H_4·OMe). The arsine is dimorphic, having two forms,

m. p. 69—70° and 91—92°; the first form was obtained only in the initial experiment, and when it had once been converted into the second form, all subsequent preparations gave the higher melting and more stable form.

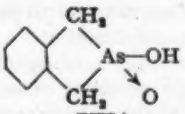
Many attempts to demethylate the *p*-anisylarsine, in order to obtain 2-*p*-hydroxyphenyl*iso*arsindoline (I; R = *p*-C_6H_4·OH), failed, but revealed a remarkable reaction. When the anisylarsine was heated with hydriodic acid of constant b. p. under the usual conditions, the product was the colourless crystalline 2-*iodo*iso*arsindoline* (V), the aryl group having been removed from the molecule; this reaction is apparently general for the 2-aryl*iso*arsindolines, since the iodoarsine (V) was similarly obtained from the 2-phenylarsine (I; R = Ph). Now although *p*-anisylphosphines when heated with hydriodic acid undergo smooth demethylation without fission of the P–C bonds (Davies and Mann, *J.*, 1944, 276), *p*-anisylarsines under these conditions are usually converted ultimately into arsenic tri-iodide (Michaelis and Weitz, *Ber.*, 1887, **20**, 48). The fact that our 2-*aryl*iso*arsindolines* even under the prolonged effect of boiling hydriodic acid gave the iodoarsine (V), and that no further fission of the As–C bonds occurred, is striking evidence of the stability of the cyclic *iso*arsindoline system.



(V.)



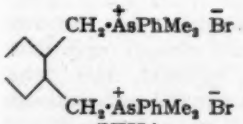
(VI.)



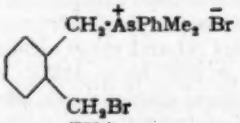
(VII.)

The iodoarsine (V) has many interesting reactions; for example with sodium sulphide it forms the highly crystalline *bis*-2-iso*arsindolyl sulphide* (VI), whereas oxidation and hydrolysis furnish o-*xylylenearsinic acid* (VII). Its greatest value is that by reaction with an appropriate Grignard reagent other aryl or alkyl groups can be inserted in the 2-position, and a very convenient method of converting one tertiary *iso*arsindoline into another is thus available (*vide infra*).

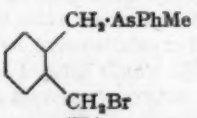
The use of sodium in the initial formation of 2-aryl*iso*arsindolines (I) imposes severe limitation upon the nature of the substituents which can be introduced into the 2-aryl group and (possibly more important) into the *o*-phenylene radical. To overcome this difficulty, we have in our later work devised an alternative synthesis of these *iso*arsindolines (I). When phenyldimethylarsine is added to an equimolecular quantity of *o*-xylylene dibromide, quaternary salt formation readily occurs, and when the product is heated under reduced pressure methyl bromide is lost and ultimately crude 2-phenyl*iso*arsindoline (I; R = Ph) distils in *ca.* 60% yield. The precise course of this reaction is uncertain. The initial product is a mixture of arsonium bromides, of which we have been able to identify only *o*-xylylene bis(phenyldimethylarsonium bromide) (VIII) in the form of its *dipicrate*, although phenyl-*o*-bromomethylbenzyldimethylarsonium bromide (IX) is probably also present. The residue after the distillation



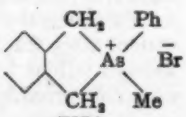
(VIII.)



(IX.)



(X.)



(XI.)

contains the more stable phenyltrimethylarsonium bromide, $PhMe_3AsBr$. It is clear therefore that a number of reactions occur during the heating. The compound (VIII) may dissociate, regenerating phenyldimethylarsine and forming (IX), which can then lose methyl bromide to give either the tertiary arsine (X) or 2-phenyl-2-methyl*iso*arsindolinium bromide (XI), either of which by subsequent further loss of methyl bromide would produce 2-phenyl*iso*arsindoline (I; R = Ph). Alternatively, it is possible that (VIII) decomposes with initial loss of methyl bromide and then phenyldimethylarsine, forming ultimately phenyltrimethylarsonium bromide and the *iso*arsindolinium bromide (XI), which then gives the *iso*arsindoline.

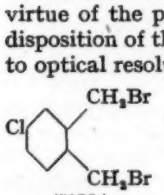
This new synthetic route is probably susceptible to wide development. In addition to allowing the introduction of groups which would be affected by metallic sodium, it does not require the prolonged precautions against arsine oxidation that the sodium condensation method demands, it is much shorter than this method, and its yields are considerably higher. Furthermore, it is probable that the initial use of trimethylarsine instead of phenyldimethylarsine would similarly afford 2-methyl*iso*arsindoline (I; R = Me).

The therapeutic activities of the three 2-aryl*iso*arsindolines (I; R = *p*-C_6H_4Me, *p*-C_6H_4Cl,

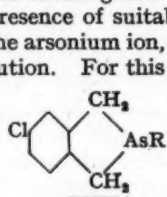
p-C_6H_4·OMe), in the form of their dihydroxides or oxides, have been tested by Dr. D. G. Davy in the Biological Laboratories of Imperial Chemical Industries Ltd., Blackley, Manchester; these compounds prove to have activities against *T. congolense* not appreciably higher than that of 2-phenyl*iso*arsindoline dihydroxide itself. It would appear therefore that the introduction of other groups more reactive chemically (such as OH, OAc, NH_2, NHAc) into the 2-aryl or the *o*-phenylene radicals may be necessary before this activity is increased. The introduction of such groups may now be possible by our second preparative method. It is noteworthy that the presence of the *o*-phenylene radical appears to be essential for this therapeutic activity, since phenyldimethylarsine oxide showed no activity against *T. congolense*; furthermore, the presence of the 2-aryl group would also appear to be necessary, for the arsonic acid (VII) also proved to be similarly inactive.

We have attempted to prepare 2-phenyl*iso*stibindoline by the interaction of *o*-xylylene dibromide, phenyldichlorostibine, and sodium in boiling ether, with the usual addition of ethyl acetate as a catalyst (Lyon and Mann, *loc. cit.*), but the only antimony derivative isolated was triphenylstibine, which had evidently been formed by dismutation of the dichlorostibine. We are now attempting to prepare the *iso*stibindoline by a method parallel to our second synthesis of the *iso*arsindolines.

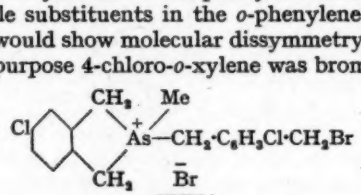
We have also investigated the synthesis of a spirocyclic bis*iso*arsindolium salt which, by virtue of the presence of suitable substituents in the *o*-phenylene groups and the tetrahedral disposition of the arsonium ion, would show molecular dissymmetry and therefore be susceptible to optical resolution. For this purpose 4-chloro-*o*-xylene was brominated to 4-*chloro*-o-*xylylene*



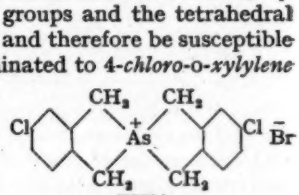
(XII.)



(XIII.)



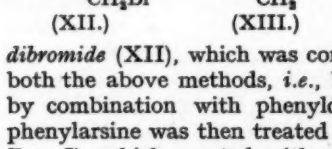
(XIV.)



(XV.)

dibromide (XII), which was converted into *5-chloro-2-phenyliso**arsindoline*** (XIII; R = Ph) by both the above methods, *i.e.*, by heating with phenyldichloroarsine and sodium in ether, and by combination with phenyldimethylarsine and subsequent thermal decomposition. The phenylarsine was then treated with hydriodic acid to form *5-chloro-2-iodoiso**arsindoline*** (XIII; R = I), which reacted with methylmagnesium iodide to give *5-chloro-2-methyliso**arsindoline*** (XIII, R = Me). This methylarsindoline was prepared by this circuitous route rather than by, for example, the direct action of methyldichloroarsine and sodium on the dibromide (XII) because previous experience (Lyon and Mann, *loc. cit.*) indicated that a higher overall yield of the final product would thus be obtained. The methyl*iso*arsindoline was then combined with the dibromide (XII) to form *5-chloro-2[4-(or 5)-chloro-2-bromomethylbenzyl]-2-methyliso**arsindolinium bromide*** (XIV), which when heated at 160—170°/15 mm. very readily furnished the highly crystalline As-spiro-*bis*-*5-chloro*iso*arsindolinium bromide* (XV).

This bromide was converted into the corresponding d-*bromocamphorsulphonate*, crops of which, after fractional crystallisation from methyl and ethyl alcohol under various conditions, showed values for $[M]_D$ which ranged from + 278° to + 318°. When, however, these crops were converted by the action of calcium or sodium iodide in cold solution into the *arsindolinium iodide*, the latter was inactive. The d-*camphorsulphonate*, when submitted to similar fractional crystallisation, gave various crops whose rotations never differed appreciably from that required for the sulphonate ion alone, and which also gave in turn the inactive *iodide*.



(XVI.)

In view of these results it was judged inadvisable in subsequent experiments to isolate the spirocyclic arsonium ion as the iodide after attempted resolution, since there was a possibility that one of the heterocyclic rings in the iodide might undergo fission to give the isomeric tertiary arsine (XVI) with consequent immediate racemisation, although no evidence of such fission could be detected.

In order to obtain a salt entirely different in type from the above sulphonates, the racemic arsonium bromide was treated with silver *l-N*-1-phenylethylphthalamate (Mann and Watson, this vol., p. 505), and thus converted into the spiro-*arsindolinium* l-N-1-*phenylethylphthalamate*, $[(C_8H_7Cl)_2As]$·O_2C·C_6H_4·CO·NH·CHPhMe. This salt separated from aqueous alcohol initially as fine crystals of the *monohydrate*, which melted indefinitely between 60° and 100° and therefore appeared to be a diastereoisomeric mixture. After one crystallisation from aqueous alcohol, the monohydrate had m. p. 144—145° (unchanged by dehydration) and was inactive in alcoholic solution. Two more recrystallisations left the m. p. unchanged, but the salt now had $[\alpha]_D$ + 2·7°

in alcoholic solution: this rotation was unchanged for two days, but the solution when then evaporated in a desiccator at room temperature deposited the phthalamate having m. p. 110—125°. When this feebly dextro-rotatory phthalamate was treated in ice-cold alcoholic solution with sodium thiocyanate, the crystalline inactive *arsindolinium thiocyanate* was deposited. The preparation of the *l*-phthalamate was repeated and the initial crop of this salt had m. p. 68—115°, increased to 137—139° and to 144—145° by two further recrystallisations. The final product had no detectable activity in alcoholic solution, and when treated with picric acid in cold concentrated alcoholic solution deposited the inactive *arsindolinium picrate*. That racemisation of the phthalamate ion (intrinsically very improbable) had not occurred was shown by the fact that the mother-liquors from the precipitation of the picrate—which must have contained the phthalamic acid—were markedly lævo-rotatory.

No fully satisfactory explanation of these data can be suggested. The inactivity (or very weak dextro-rotation) of the arsonium *l*-phthalamate would indicate that the recrystallisation had caused the resolution to proceed until the arsonium ion had a dextro-rotation almost equal to the lævo-rotation of the phthalamate ion. This would imply an almost instantaneous racemisation of the arsonium ion when it was subsequently precipitated as the thiocyanate or picrate. There is no obvious mechanism for racemisation of the arsonium ion, other than the opening of one ring described above, and such a reaction would be improbable for the thiocyanate and exceedingly improbable for the picrate. Furthermore, the homologous active *As-spiro*-bis-1 : 2 : 3 : 4-tetrahydro*iso*arsinolinium ion (Holliman and Mann, *J.*, 1945, 45) gave no indication of racemisation in solution. In view of these results, and of the small supply of material, these attempts at resolution were abandoned.

Experimental.

All compounds, unless otherwise stated, were colourless. Solvents used for recrystallisation are given in parenthesis after the compounds concerned. All rotations were determined in a 4-dcm. tube, the source of light being the sodium D line (λ 5893). The m. p.'s of many of the hydroxynitrates were dependent on the rate of heating, and the recorded values are those obtained when the material was placed in a bath at about 10° below the m. p., and the temperature then increased.

2-Arylisoarsindolines and Derivatives.—(1) *2-Phenylisoarsindoline* (I; R = Ph). The preparation by the sodium method has been described (Lyon and Mann, *loc. cit.*). The first two of the following three experiments were performed to indicate the nature of the intermediate products in the arsonium bromide method, and the third on a larger scale to determine the yield of the *iso*arsindoline. The phenyldimethylarsine was prepared in 90% yield by the action of methylmagnesium iodide on phenyldichloroarsine (Winmill, *J.*, 1912, **101**, 722), and was characterised by reaction with potassium palladochloride, whereby *dichlorobis(phenyldimethylarsine)palladium*, orange leaflets from alcohol, m. p. 170—173° (Found: C, 35·5; H, 4·2. $C_{16}H_{22}Cl_2As_2Pd$ requires C, 35·45; H, 4·1%), was obtained.

(i) A solution of *o*-xylylene dibromide (0·94 g.) in benzene (5 c.c.) was added to phenyldimethylarsine (0·65 g., 1 mol.) in a flask filled with carbon dioxide. The mixture was refluxed for 1 hour in a stream of carbon dioxide and the benzene then removed. The residue formed a very deliquescent glass which could not be crystallised. It was therefore dissolved in water and treated with sodium picrate, whereby *o-xylylene bis(phenyldimethylarsonium picrate)* (as VIII) was obtained, yellow crystals, m. p. 163·5—164·5°, after two recrystallisations (alcohol–acetone) (Found: C, 46·5; H, 3·35; N, 9·2. $C_{36}H_{34}O_{14}N_6As_2$ requires C, 46·7; H, 3·7; N, 9·1%).

(ii) Phenyldimethylarsine (0·36 g.) was run slowly into a solution of the dibromide (0·52 g., 1 mol.) in benzene, which was then slowly distilled in a current of carbon dioxide. The resulting glass was extracted with water, leaving a residue of unchanged dibromide (0·15 g., 30%). The aqueous extract gave the above picrate (0·4 g., 22%), m. p. 163·5—164·5° after recrystallisation, unchanged by admixture with the previous sample.

(iii) The dibromide (36·1 g.) was carefully added to a solution of phenyldimethylarsine (25·1 g.) in chloroform (40 c.c.) in a distilling flask through which a stream of carbon dioxide was passed. The chloroform was removed by distillation, and the residue then heated at 17 mm. pressure. Considerable foaming ensued as methyl bromide was evolved. Ultimately the product was heated at 180°/17 mm. for 2 hours, during which period a small amount of the unchanged dibromide distilled over, and colourless crystals separated in the residual product. The latter was then heated at 0·5 mm., and the crude 2-phenyl*iso*arsindoline (20·9 g., 59% yield based on the arsine) was obtained as the main fraction, b. p. 140—155°. The distillate when set aside formed two layers. The top layer (7·3 g.) on oxidation gave 2-phenyl*iso*arsindoline hydroxynitrate (crude, 9·0 g.; recrystallised, 4·4 g.; m. p. 147—148° (effer.); the lower layer (13·6 g.) also gave the hydroxynitrate (crude, 14·1 g.; recrystallised, 4·3 g.). The *iso*arsindoline was further characterised by conversion into the methiodide and methopicrate, both identical with products prepared by Lyon and Mann (*loc. cit.*).

The residue after the distillation, when recrystallised (alcohol), furnished phenyltrimethylarsonium bromide (3·3 g.), m. p. 281° (decomp.) (Found: C, 39·2; H, 5·1. Calc. for $C_9H_{14}BrAs$: C, 39·0; H, 5·05%), giving the picrate, yellow needles, m. p. 140—141·5° (Found: C, 42·4; H, 4·1; N, 10·0. Calc. for $C_{15}H_{16}O_7N_3As$: C, 42·3; H, 3·8; N, 9·9%). Steinkopf and Schwen (*Ber.*, 1921, **54**, 1437) give m. p. 284° (decomp.) and 145° respectively.

A repetition of the above experiment, in which the phenyldimethylarsine was now added to the dibromide, gave a similar result; yield of pure hydroxynitrate, 20%.

(2) 2-p-*Tolyl*isoarsindoline (I; R = *p*-C_6H_4Me). A solution of *p*-tolyldichloroarsine (47·4 g.) in dry ether (200 c.c.) was slowly added with cooling to a solution of *o*-xylylene dibromide (52·8 g., 1 mol.) in ether (400 c.c.) containing fine sodium wire (40 g.), the apparatus employed being that already described (Lyon and Mann, *loc. cit.*). Cautious addition of the dichloroarsine was particularly necessary in this series, because the arsine reacts very vigorously and rapidly with the sodium. Ethyl acetate (5 c.c.) was then added and the mixture gently refluxed for 9 hours, further quantities of ethyl acetate (2 c.c. and 3 c.c.) being added after 4 and 6·5 hours' heating. After filtration of the solution under pressure followed by distillation of the ether in a nitrogen atmosphere as previously described, the sticky black residue on fractionation gave the crude arsine, b. p. 132—137°/0·05 mm.; 10 g., 19%.

For purification, the arsine (10 g.) was slowly added with stirring to concentrated nitric acid (*ca.* 50 c.c.) chilled in ice–water. When oxidation was complete, the *hydroxynitrate* (II; R = *p*-C_6H_4Me, X = NO_3) was precipitated by the addition of water, collected, and recrystallised (dilute nitric acid); m. p. 146—146·5° (effer. with preliminary softening) (Found: C, 51·6; H, 4·7; N, 4·2. $C_{15}H_{16}O_4NAs$ requires C, 51·6; N, 4·6; N, 4·0%); 9 g. (13%). This compound readily gave the *hydroxypicrate*, light feathery yellow crystals (alcohol), m. p. 147° (Found: C, 48·8; H, 3·6; N, 8·45. $C_{21}H_{18}O_8N_3As$ requires C, 48·9; H, 3·5; N, 8·2%).

The above hydroxynitrate (8 g.) was shaken with excess of 5% aqueous sodium hydroxide and extracted with chloroform. The dried chloroform layer on evaporation gave the viscous oily *arsine oxide* (III; R = *p*-C_6H_4Me) which solidified in a vacuum over phosphoric anhydride and then, being very hygroscopic, was rapidly crystallised (xylene); m. p. 134—136° (Found: C, 62·65; H, 5·6. $C_{15}H_{15}OAs$ requires C, 62·9; H, 5·3%). The oxide on exposure to air rapidly absorbed water, liquefied, and subsequently resolidified to the non-hygroscopic *arsine dihydroxide hemihydrate* (II; R = *p*-C_6H_4Me, X = OH): m. p. 53—54° (Found: C, 57·4; H, 5·8. $C_{15}H_{17}O_2As,\frac{1}{2}H_2O$ requires C, 57·5; H, 5·8%).

To obtain the pure arsine, the hydroxynitrate (10 g.) was shaken as before with dilute sodium hydroxide solution and chloroform, and the latter (*ca.* 100 c.c.) then separated, mixed with dilute hydrochloric acid (1 : 10 by vol., 150 c.c.) containing potassium iodide (0·1 g.), and saturated with sulphur dioxide for 2 hours. Distillation then gave the pure 2-p-*tolyl*isoarsindoline (I; R = *p*-C_6H_4Me), b. p. 138—139°/0·3 mm. (Found: C, 67·0; H, 6·0. $C_{15}H_{15}As$ requires C, 66·7; H, 5·6%); 7 g. When a mixture of this arsine and methyl iodide was refluxed for 30 minutes and then set aside in an open dish, large crystals of 2-p-*tolyl*-2-*methyl*isoarsindolinium *iodide* ultimately formed, m. p. 156° after recrystallisation (alcohol) (Found: C, 46·7; H, 4·6; I, 31·2. $C_{16}H_{18}IAs$ requires C, 46·6, H, 4·4; I, 30·8%). This salt formed the corresponding *picrate*, yellow needles (alcohol), m. p. 134—135° (Found: C, 51·6; H, 4·2; N, 8·4. $C_{28}H_{20}O_7N_3As$ requires C, 51·45; H, 3·9; N, 8·2%).

(3) 2-p-*Chlorophenyl*isoarsindoline (I; R = *p*-C_6H_4Cl). *p*-Chlorophenyldichloroarsine was prepared from the arsonic acid (Hunt and Turner, *J.*, 1925, **127**, 2671) and obtained as a colourless liquid, b. p. 110—115°/0·1 mm.

A solution of the dichloroarsine (51·5 g.) in ether (100 c.c.) was added to one of *o*-xylylene dibromide (52·8 g., 1 mol.) containing sodium wire (23 g.), and the mixture refluxed for 14 hours with additions of ethyl acetate (5 c.c.) every 4 hours. The usual treatment then gave a black oil which on distillation furnished three fractions: (*a*) b. p. 106—168°/0·1 mm., (*b*) b. p. 168—175°/0·05 mm., (*c*) b. p. 175—187°/0·05 mm. (5·8 g.). Fraction (*c*) contained the crude arsine, fractions (*a*) and (*b*) only by-products.

The crude arsine was oxidised as usual with nitric acid, but the crude sticky *hydroxynitrate* (II; R = *p*-C_6H_4Cl, X = NO_3) which separated on the addition of water had to be kneaded repeatedly with ether before it formed a clean white solid; recrystallisation (dilute nitric acid) then gave the pure salt, m. p. 144—145° (effer.) dependent on rate of heating (Found: C, 45·4; H, 3·4; N, 3·9; Cl, 9·45. $C_{14}H_{13}O_4NClAs$ requires C, 45·5; H, 3·5; N, 3·8; Cl, 9·6%). This salt gave the *hydroxypicrate*, yellow crystals (alcohol), m. p. 147—148° with preliminary softening (Found: C, 45·1; H, 2·6; N, 7·9. $C_{20}H_{12}O_8N_3ClAs$ requires C, 44·8; H, 2·8; N, 7·85%).

The usual treatment of the hydroxynitrate with sodium hydroxide solution and chloroform gave the oily *oxide* (III; R = *p*-C_6H_4Cl) which readily solidified and was then recrystallised (ethyl carbonate); m. p. 145—146° dependent on rate of heating (Found: C, 54·4; H, 3·84; Cl, 11·4. $C_{14}H_{12}OClAs$ requires C, 54·8; H, 3·95; Cl, 11·6%). The oxide although slightly hygroscopic was not very soluble in cold water; recrystallisation from hot water gave the *dihydroxide hemihydrate* (II; R = *p*-C_6H_4Cl, X = OH), m. p. 77—78° with preliminary softening (Found: C, 50·0; H, 4·7. $C_{14}H_{14}O_2ClAs,\frac{1}{2}H_2O$ requires C, 50·4; H, 4·5%). The dihydroxide was readily converted into the oxide in a vacuum desiccator.

The pure 2-p-*chlorophenyl*isoarsindoline, prepared in the usual way from the pure hydroxynitrate, was obtained as a colourless liquid, b. p. 153—154°/0·05 mm., which readily solidified and after crystallisation (alcohol) had m. p. 63—64° (Found: C, 57·7; H, 4·0; Cl, 11·9. $C_{14}H_{12}ClAs$ requires C, 57·8; H, 4·2; Cl, 12·2%). This arsine formed a *methiodide*, needles (alcohol), m. p. 204° (Found: C, 41·3; H, 3·4. $C_{15}H_{15}ClIAs$ requires C, 41·6; H, 3·5%), which in turn afforded a *methopicrate*, long yellow needles (water), m. p. 162° (Found: C, 47·6; H, 3·4. $C_{21}H_{17}O_7N_3ClAs$ requires C, 47·2; H, 3·2%).

(4) 2-p-*Anisyl*isoarsindoline (I; R = *p*-C_6H_4·OMe). Although the preparation of *p*-anisylarsonic acid has been previously described (Michaelis and Weitz., *Ber.*, 1887, **20**, 48; Schmidt, *Annalen*, 1920, **421**, 169; Adams *et al.*, *J. Amer. Chem. Soc.*, 1922, **44**, 1371; 1923, **45**, 1312), the following modifications improve the preparation. A solution of *p*-anisidine (184 g., 2 mols.) in a mixture of water (1·5 l.) and concentrated hydrochloric acid (375 c.c., 5 mols.) was diazotised at 0° by slow addition of sodium nitrite (104 g., 2 mols.) in water (200 c.c.). Meanwhile a mixture of arsenious oxide (178 g., 1·2 mols.), anhydrous sodium carbonate (330 g., *ca.* 4 mols.), hydrated copper sulphate (20 g.), and water (750 c.c.) was heated to boiling (it remained turbid) and then cooled to 17°. The diazo-solution was then added slowly to the well-stirred arsenite solution, benzene being occasionally added to prevent frothing. The complete mixture was then stirred for 6 hours, set aside overnight, filtered, cooled to 0°, and acidified by running in dilute hydrochloric acid with vigorous stirring; provided this operation was performed slowly the crude arsonic acid (222 g., 64%) separated with very little tar, could be readily collected on a filter, and was pure enough for the next stage.

Sulphur dioxide was passed into a mixture of the arsonic acid (100 g.), concentrated hydrochloric acid (200 c.c.), and potassium iodide at 0° for 1 hour. During the reduction benzene was added to dissolve the considerable amount of solid matter that was precipitated. Ultimately the benzene layer was separated, dried (Na_2SO_4), and distilled, *p*-anisyldichloroarsine being obtained as a pale pink oil, b. p. 138·5—139°/0·5 mm. which readily solidified and then had m. p. 47—48°; 75 g. (69%) (*cf.* Michaelis and Weitz, *loc. cit.*; Blicke *et al.*, *J. Amer. Chem. Soc.*, 1929, **51**, 3480; 1937, **59**, 536). If the reduction is performed at 100°, anisole and arsenic tri-iodide result.

To prepare the arsindoline, solutions of the dichloroarsine (50·6 g.) in ether (200 c.c.) and of *o*-xylylene dibromide (52·8 g., 1 mol.) in ether (400 c.c.) containing sodium (40 g.) were mixed and refluxed for 13 hours with the usual addition of ethyl acetate. Careful fractionation of the usual tarry residue then gave 2-p-*anisyliso**arsindoline* (I; R = *p*-C_6H_4·OMe) (7 g., 12%) as a colourless liquid, b. p. 167—168°/0·03 mm., which readily solidified in the receiver and when first recrystallised (alcohol) had m. p. 69—70°, but when subsequently recrystallised or prepared had always m. p. 91—92° (Found: C, 63·2; H, 5·4; *M*, cryoscopic in 0·99% benzene solution, 272; in 2·26% solution, 287. $C_{15}H_{15}OAs$ requires C, 62·9; H, 5·3; *M*, 286). The arsine readily formed a *methiodide*, thick heavy plates (alcohol), m. p. 148° with preliminary softening (Found: C, 45·3; H, 4·5; I, 29·9. $C_{16}H_{18}OIAs$ requires C, 44·9, H, 4·2; I, 29·7%), which gave a *methopicrate*, yellow needles (alcohol), m. p. 134° (Found: C, 49·9; H, 3·7; N, 8·1. $C_{22}H_{20}O_8N_3As$ requires C, 49·9; H, 3·8; N, 7·9%).

The arsine also gave a *hydroxynitrate* (II; R = *p*-C_6H_4·OMe; X = NO_3), m. p. 141° (effer., preliminary softening) after recrystallisation (dilute nitric acid) (Found: C, 49·4; H, 4·6; N, 3·8. $C_{15}H_{16}O_5NAs$ requires C, 49·3; H, 4·4; N, 3·8%); this salt in turn furnished a *hydroxypicrate*, hard yellow crystals (alcohol), m. p. 159° (preliminary softening) (Found: C, 47·7; H, 3·3; N, 7·8. $C_{21}H_{18}O_9N_3As$ requires C, 47·4; H, 3·4; N, 7·9%).

The hydroxynitrate was converted by the usual treatment into the *oxide* (III; R = *p*-C_6H_4·OMe), needles (ethyl carbonate), m. p. 150—151°, unchanged by confinement in a vacuum over sulphuric acid (Found: C, 59·4; H, 4·8. $C_{15}H_{15}O_2As$ requires C, 59·6; H, 5·0%). The oxide when exposed to air slowly formed a viscous syrup, from which no crystalline dihydroxide could be isolated.

p-*Nitrophenyldichloroarsine.*—Sulphur dioxide was passed for 30 minutes through a solution of *p*-nitrophenylarsonic acid (20 g.) in cold concentrated hydrochloric acid (75 c.c.) containing potassium iodide (0·1 g.). The resultant yellow oil, when collected, dried (Na_2SO_4), and distilled, gave the liquid *chloroarsine*, b. p. 189°/0·4 mm. (Found: Cl, 26·6. $C_6H_4O_2NCl_2As$ requires Cl, 26·5%). Blicke *et al.* (*loc. cit.*) mention this preparation, but do not cite b. p. or analyses for the compound.

Many attempts were made to condense this dichloroarsine with *o*-xylylene dibromide in the presence of sodium in the usual way, but distillation of the final ethereal solution gave a minute residue which charred extensively on attempted distillation.

2-*Iodoisoarsindoline* (V).—2-Phenyl*iso*arsindoline, prepared as above from the hydroxynitrate and isolated from the chloroform extract without distillation, was at once heated with hydriodic acid (50 c.c., constant b. p.) at 120—130° for 2 hours in a stream of carbon dioxide. Initially the arsine floated on the surface but towards the end of the reaction it sank; consequently repeated shaking of the reaction mixture was necessary. After cooling to 0°, the solid *iodo*-compound (V) was collected, rapidly drained (since the crude product darkens on exposure to air) and recrystallised (alcohol); pale yellow plates, m. p. 107—108°, unaffected by subsequent crystallisation from light petroleum (b. p. 80—100°) (Found: C, 31·8; H, 3·1; I, 41·6. C_6H_6IAs requires C, 31·4; H, 2·6; I, 41·5%): 7·5 g. Precisely similar results were obtained when the 2-*p*-anisylarsine was used.

When the crude powdered iodide was stirred with aqueous sodium carbonate solution for 1 hour, a white solid (presumably the hydroxy-arsine) was obtained, but could not be recrystallised. When concentrated hydrochloric acid was added to its hot alcoholic solution, cooling and scratching gave 2-*chloroisoarsindoline* (as V), which when recrystallised from alcohol containing hydrochloric acid formed white crystals, m. p. 73—74° (Found: C, 44·7; H, 3·8; Cl, 16·6. C_8H_8ClAs requires C, 44·8; H, 3·8; Cl, 16·5%).

When a mixture of the powdered iodide and 5% aqueous sodium hydroxide was boiled for a few minutes, cooled, and just acidified with sulphuric acid, a white precipitate (of the hydroxide) was again formed. This was dissolved in chloroform and saturated with hydrogen sulphide; filtration and evaporation then gave an oil which readily solidified, and when recrystallised (alcohol) furnished *bis*-2-*isoarsindolyl sulphide* (VI), magnificent white crystals, m. p. 146°, dependent on rate of heating (Found: C, 49·3; H, 4·3; S, 8·2. $C_{16}H_{14}SAs_2$ requires C, 49·2; H, 4·1; S, 8·2%).

o-*Xylylenearsinic Acid* (VII).—Concentrated nitric acid was added dropwise to a mixture of the powdered iodo-arsine (7·5 g.) and water (50 c.c.). The mixture was gently warmed to volatilise the liberated iodine, and the addition of the acid continued until this liberation ceased; finally the mixture was boiled to remove the last traces of iodine and then cooled, when the *arsinic acid nitrate*, $C_6H_4<[CH_2]_2>As(OH)_2NO_3$, separated as white crystals (4·5 g.) which when collected and washed with ether had m. p. 123—124° (effer., preliminary softening), unchanged by recrystallisation from acetone (Found: C, 35·4; H, 3·6; N, 5·4. $C_8H_{10}O_5NAs$ requires C, 34·9; H, 3·7; N, 5·1%).

A mixture of N-sodium hydroxide (16·3 c.c.), the nitrate (4·48 g., 1 equivalent), and water (50 c.c.) was heated until clear and then cooled; the fine needles of the *monohydrated arsinic acid* (VII) which separated were collected and recrystallised (water); m. p. 144° (decomp.) (Found: C, 41·8; H, 5·1. $C_8H_9O_3As,H_2O$ requires C, 41·7; H, 4·8%).

Attempted Preparation of 2-Phenylisostibindoline.—A solution of phenyldichlorostibine (54 g.) in ether (300 c.c.) was added to one of *o*-xylylene dibromide (52·8 g., 1 mol.) in ether (400 c.c.) containing sodium wire (40 g.) and the mixture refluxed for 12 hours in a nitrogen atmosphere with the usual periodic additions of ethyl acetate. The normal filtration and distillation then gave a main fraction, b. p. 200—260°/0·5 mm. (chiefly 240°) (10 g.). A portion of this oil was cautiously oxidised with cold concentrated nitric acid; dilution with water gave a sticky solid which when kneaded with ether formed a clear white powder. A solution of this material in a large volume of boiling water was filtered and nitric acid (0·5 c.c.) added. On cooling, crystals of *bis(triphenylstibine) oxide dinitrate*, $(Ph_3Sb)_2O(NO_3)_2$,

m. p. 226—227° (effer.), unchanged by two further recrystallisations, separated (Found: C, 51·1, 50·8; H, 3·4, 3·6; N, 3·4. $C_{38}H_{30}O_7N_2Sb_2$ requires C, 51·1; H, 3·6; N, 3·3%). The duplicate analyses are of the products of two different experiments and are given to indicate the consistent composition of our product, since Morgan, Micklethwait, and Whitby (*J.*, 1910, **97**, 36) assert that triphenylstibine hydroxynitrate (which requires C, 50·2; H, 3·7; N, 3·3%) softens at 220° and melts at 224—225° (decomp.).

When concentrated hydrochloric acid was added to a hot alcoholic solution of the oxide-dinitrate, triphenylstibine dichloride separated in long needles, which after recrystallisation (alcohol containing a few drops of concentrated hydrochloric acid) had m. p. 141·5—142·5° (Found: C, 51·1; H, 3·6. Calc. for $C_{18}H_{15}Cl_2Sb$: C, 51·0; H, 3·6%). Michaelis and Reece (*Ber.*, 1882, **15**, 2876; *Annalen*, 1886, **233**, 39) give m. p. 143°.

4-Chloro-o-xylene.—This compound has previously been obtained only by direct chlorination (Kruger and Claus, *Ber.*, 1885, **18**, 1755; Baeyer, *Annalen*, 1893, **274**, 305). A solution of 4-amino-*o*-xylene (121 g.) in a warm mixture of concentrated hydrochloric acid (227 c.c.) and water (227 c.c.) was rapidly cooled so that fine crystals of the hydrochloride separated. Crushed ice (200 g.) was then added, and the temperature kept below 10° whilst a solution of sodium nitrite (77·2 g.) in water (182 c.c.) was slowly added with stirring. Meanwhile, a solution of sodium bisulphite (63·5 g.) in water (115 c.c.) was added to a solution of hydrated copper sulphate (127 g.) and sodium chloride (43 g.) in water (550 c.c.) at 60°. The mixture was cooled and the cuprous chloride collected, washed with water, and quickly transferred to a 2-l. flask containing concentrated hydrochloric acid (91 c.c.) and water (91 c.c.), and fitted with a reflux condenser and dropping funnel. The flask was heated on a boiling water-bath whilst a fine stream of the diazo-solution was run in with occasional shaking. The final product was steam-distilled, and the distillate basified and extracted with ether. The extract was shaken with aqueous sodium hydroxide solution, dried, and distilled. The fraction b. p. 190—200° on redistillation gave pure 4-chloro-*o*-xylene, b. p. 193—197°; 75 g. (53%).

4-Chloro-o-xylylene Dibromide (XII).—Bromine (107·6 c.c., 2 mols.) was slowly added to 4-chloro-*o*-xylene (150 g.) by means of a delivery tube which dipped below the surface of the xylene; the latter meanwhile was maintained at 125—130°. Addition of the bromine was necessarily slow (*ca.* 6 hours) because otherwise much unchanged bromine would have escaped with the hydrogen bromide evolved. When the addition was complete, heating was continued at atmospheric pressure for 1 hour, and then at *ca.* 15 mm. to remove readily volatile products. Slow distillation then gave the fractions: (i) b. p. 80—85°/0·1 mm., (ii) b. p. 85—112°/0·1 mm., (iii) b. p. 112°/0·1 mm.—130°/0·2 mm. (*ca.* 200 g.), (iv) b. p. 130—138°/0·2 mm. Fraction (iii) when distilled through a 30 cm. column gave the fractions: (*a*) b. p. 100—111°/0·1 mm., (*b*) b. p. 111—127°/0·1 mm. Fraction (*b*) (129 g., 40%) slowly solidified and when recrystallised (alcohol) afforded the *dibromide* (XII), m. p. 46—47° (Found: C, 31·9; H, 2·2. $C_8H_7ClBr_2$ requires C, 32·2; H, 2·4%).

Fraction (i) also solidified, and when recrystallised (alcohol) gave 3(or 4)-*chloro-o-xylyl bromide*, m. p. 37—38° (Found: C, 43·7; H, 3·7. C_8H_8ClBr requires C, 43·75; H, 3·7%). This compound liquefied when mixed with the dibromide (XII).

5-Chloro-2-phenylisoarsindoline (XIII; R = Ph).—(1) *By the sodium reaction.* A solution of phenyldichloroarsine (50 g., 1·2 mols.) in ether (200 c.c.) was added to one of the dibromide (XI) (55 g., 1 mol.) in ether (400 c.c.) containing sodium wire (22 g.), and the mixture refluxed for 10 hours in a nitrogen atmosphere with the usual periodic additions of ethyl acetate. Filtration and distillation at 0·2 mm. then gave the fractions: (i) b. p. 80—110°, (ii) b. p. 110—150°; (iii) b. p. 150—180°. Fraction (i) was unchanged dichloroarsine, (iii) was the crude arsindoline (20 g.) boiling mainly at 155—165°/0·2 mm., and fraction (ii) was of negligible quantity.

The arsindoline (20 g.) was purified by the usual conversion into the hydroxynitrate, which, after precipitation by the addition of water, was collected, thoroughly washed with ether, and dissolved in boiling water (400—500 c.c.); concentrated nitric acid (20 c.c.) was added to the filtered solution, which was immediately cooled in ice–water. The pure *hydroxynitrate* (11 g.) which separated was washed with alcohol and ether; m. p. 143·5° (effer.) unchanged by crystallisation (alcohol) (Found: C, 45·3; H, 3·6; N, 3·7; Cl, 9·8. $C_{14}H_{13}O_4NClAs$ requires C, 45·5; H, 3·55; N, 3·8; Cl, 9·6%). This salt formed a *hydroxypicrate*, pale yellow crystals (alcohol), m. p. 154—155° with preliminary softening (Found: C, 45·0; H, 2·7; N, 7·8. $C_{20}H_{16}O_{11}N_4ClAs$ requires C, 44·8; H, 2·8; N, 7·85%).

The hydroxynitrate was treated as usual with aqueous sodium hydroxide and chloroform, and the latter then saturated with sulphur dioxide to reduce the arsine oxide. Distillation of the dried chloroform left the pure iso*arsindoline* (XIII; R = Ph) as a colourless liquid which did not solidify even after prolonged confinement in a desiccator (Found: C, 58·0; H, 4·6. $C_{14}H_{12}ClAs$ requires C, 57·8; H, 4·2%).

(2) *By the arsonium salt reaction.* The first of the following experiments indicates the nature of the intermediate product, and the second the formation of the required *iso*arsindoline. (i) The chloro-dibromide (XII) (0·74 g.) was added to phenyldimethylarsine (0·57 g., 1 mol.) in a flask filled with carbon dioxide, and the mixture warmed until it became homogeneous; it then rapidly formed a glass. This was cooled, well washed with ether, dissolved in water, and treated with sodium picrate. *4-Chloro-o-xylylene bis(phenyldimethyl arsonium picrate)* was obtained, yellow crystals (0·5 g.) after crystallisation (alcohol–acetone), m. p. 151—152° (Found: C, 45·3; H, 3·8; N, 8·8. $C_{38}H_{32}O_{14}N_6ClAs_2$ requires C, 45·1; H, 3·4; N, 8·8%).

(ii) Phenyldimethylarsine (9 g.) was slowly added to a solution of the chloro-dibromide (14·7 g., 1 mol.) in warm benzene (30 c.c.) in a flask through which carbon dioxide was passed. The benzene was distilled off, and the arsonium salt heated at 18 mm. until evolution of methyl bromide subsided. The product, heated at 0·2 mm., gave a main fraction of the crude *iso*arsindoline (XIII; R = Ph), b. p. 155—160°; 9·1 g. (63% based on arsine used). Oxidation gave the hydroxynitrate [crude, 10 g. (55%); recrystallised, 5·6 g. (31%)], m. p. 143—143·5° (mixed and unmixed). The residue in the flask after recrystallisation afforded phenyltrimethylarsonium bromide (0·85 g.), identified as before.

5-Chloro-2-iodo-isoarsindoline (XIII; R = I).—This was prepared precisely as the former iodo-arsine (V), and after recrystallisation (alcohol) had m. p. 121° (Found: C, 27·7; H, 2·1; I, 38·0. C_8H_7ClIAs requires C, 28·2; H, 2·1; I, 37·3%); yield, 42% based on hydroxynitrate used.

*5-Chloro-2-methyl*iso*arsindoline* (XIII; R = Me).—The powdered iodoarsine (6·8 g.) mixed with ether (150 c.c.) was slowly added to a well-stirred ice-cold Grignard reagent prepared from methyl iodide (11·2 g.), magnesium (2 g.), and ether (60 c.c.) under a nitrogen atmosphere. The complete mixture was refluxed for 30 minutes, cooled in ice–salt, and hydrolysed by the cautious addition of ice-cold dilute sulphuric acid (10 c.c. concentrated acid, 140 c.c. water), nitrogen being passed over the product throughout these operations. The ethereal layer was rapidly separated in a funnel previously filled with carbon dioxide, the aqueous layer was also extracted with ether, and the united ethereal extracts were dried with sodium sulphate containing anhydrous sodium carbonate to remove traces of hydrogen iodide. Distillation of the filtered extract ultimately gave the *methyl*iso*arsindoline* (XIII; R = Me) as a colourless liquid, b. p. 81°/0·1 mm. (Found: C, 46·8; H, 4·5. $C_9H_{10}ClAs$ requires C, 47·3; H, 4·4%); 3·5 g.

This arsine was characterised as its *methiodide* which was readily formed and after recrystallisation (alcohol) had m. p. 202—204°, dependent on rate of heating (Found: C, 32·2; H, 3·9; I, 34·9. $C_{10}H_{13}ClIAs$ requires C, 32·4; H, 3·5; I, 34·3%). This in turn formed the *methopicrate*, fine yellow needles (alcohol), m. p. *ca.* 270° (decomp.) (Found: C, 40·4; H, 3·35; N, 8·9. $C_{16}H_{15}O_7N_3ClAs$ requires C, 40·7; H, 3·2; N, 8·9%).

5-Chloro-2-[4(or 5)*-chloro-2-bromomethylbenzyl*]*-2-methyl*iso*arsindolinium Bromide* (XIV).—Powdered 4-chloro-*o*-xylylene dibromide (7·2 g.) was added to the above methylarsine (5·5 g., 1 mol.); the mixture, when gently warmed in a small stoppered flask, almost immediately formed a hard glass which readily fractured on cooling. For identification, a portion was powdered, thoroughly washed with ether, and dried (Found: C, 37·8; H, 3·5. $C_{17}H_{17}Cl_2Br_2As$ requires C, 38·7; H, 3·25%).

As-spiro-*Bis-5-chloro*iso*arsindolinium Bromide* (XV).—The crude bromide (XIV) (12·7 g.) was heated to 160° at 15 mm. for 30 minutes and then at 160—170°/15 mm. for 1·5 hours. Initially the bromide fused (*ca.* 110°) with gentle effervescence which steadily increased. After *ca.* 1 hour's heating the product began to crystallise, and finally only a pale brown solid remained. This was cooled, powdered under alcohol, and then washed on the filter with alcohol and then with much ether; yield, 8·5 g. The crude bromide was now dissolved in boiling water (*ca.* 1200 c.c.), and the hot solution filtered to remove a trace of insoluble lachrymatory impurity, diluted with hydrobromic acid of constant b. p. (50 c.c.), and then cooled and stirred. Crystallisation was slow and continued for several days. The *bromide* (XV) was then collected, washed with alcohol and ether, and dried; 6·5 g. (63% based on methylarsine used). A portion, recrystallised again, had m. p. 244—246° (decomp.) [Found: C, 44·4; H, 3·3; 2Cl + Br, 35·3; Br (ionic), 19·0. $C_{16}H_{14}Cl_2BrAs$ requires C, 44·45; H, 3·3; 2Cl + Br, 34·9; Br (ionic), 18·5%].

The spiro-*arsindolinium* d-*bromocamphorsulphonate*. Hot aqueous solutions of equimolecular quantities of the bromide (XV) and of silver *d*-bromocamphorsulphonate were mixed, gently boiled, filtered, concentrated to small bulk at 15 mm. pressure, and finally taken to dryness in a vacuum desiccator. The residual solid, when recrystallised from ethyl acetate, gave the d-*bromocamphorsulphonate monohydrate*, which on heating began to soften at *ca.* 130° becoming completely molten at *ca.* 150° (Found: C, 46·3; H, 4·9; S, 4·7. $C_{26}H_{38}O_4Cl_2BrSAs,H_2O$ requires C, 45·9; H, 4·45; S, 4·7%). A sample (4·25 g.) was recrystallised 6 times from ethyl alcohol; the product (1·8 g.) had m. p. 143—147° (effer.) without preliminary softening. A 0·345% solution in ethyl alcohol had α + 0·57°, [*M*] + 281° (for monohydrate).

Another sample was recrystallised 4 times from methyl alcohol; the product, which was still the monohydrate (Found: C, 46·3; H, 4·6%), on heating softened at 135° and became completely molten at 152° (effer.); a 0·338% solution in ethyl alcohol had α + 0·56°, [*M*] + 282°.

The mother-liquors from these 4 recrystallisations had deposited magnificent crystals after several days; the mother-liquors were carefully decanted, and the crystals rapidly washed with a small quantity of methyl alcohol, rapidly drained, dried, and investigated. The crystals from the first mother-liquor were still the monohydrate (Found: C, 45·6; H, 4·8%): a 0·404% solution in ethyl alcohol had α + 0·74°, [*M*] + 311°. Those from third mother-liquor had, in 0·374% solution in alcohol, α + 0·69°, [*M*] +313°. Those from the second and fourth mother-liquors were united, and in 0·389% solution in alcohol had α + 0·73°, [*M*] + 318°.

Since a slow crystallisation appeared to give the sulphonate of high rotation, a portion of the salt which had been recrystallised 6 times from ethyl alcohol and had [*M*] + 281° was dissolved in methyl alcohol so that the solution was almost saturated at room temperature. After several days, clumps of heavy crystals had separated which were quite distinct in appearance from those previously growing in cold methyl alcohol; a 0·353% solution of these heavy crystals in ethyl alcohol had α + 0·62°, [*M*] + 298°. The experiment was repeated with a second portion of the salt, and the cold methyl alcoholic solution seeded with the crystals having [*M*] + 313°; however, a crop of very fine needles resulted, and a 0·361% solution of these needles in ethyl alcohol had α + 0·59°, [*M*] + 278°.

These inconsistent values for the rotation indicated that the crops of high rotation which separated from the original methyl alcohol mother-liquors may have been partly or wholly resolved. To test this possibility, the salt having [*M*] + 318° was dissolved in a minimum amount of cold acetone containing methyl alcohol, and treated with a concentrated acetone solution of calcium iodide. The microcrystalline *arsindolinium iodide* rapidly separated, and when collected and washed in turn with acetone, water, and acetone, was colourless (Found: C, 39·8; H, 3·2. $C_{16}H_{14}Cl_2IAs$ requires C, 40·1; H, 2·9%); m. p. 258—262°. The iodide was almost insoluble in all the usual solvents except formamide; a 0·501% solution in formamide was inactive. To confirm this result, the salt having [*M*] + 313° was dissolved in cold methyl alcohol and treated with a cold concentrated sodium iodide solution also in methyl alcohol; the colourless arsindolinium iodide which separated was again inactive in 0·534% formamide solution. The insolubility of the iodide in all the common solvents affords strong evidence that it had retained the spirocyclic structure (as XV), because these physical properties, although not unexpected for such an arsonium salt, would be most improbable for the tertiary arsine (XVI).

The spiro-*arsindolinium* d-*camphorsulphonate*. A solution of silver *d*-camphorsulphonate (3·432 g.) in hot water (30 c.c.) was added to one of the above iodide (4·848 g., 1 mol.) in boiling aqueous alcohol

(450 c.c.; 3 vols. water–1 vol. alcohol), and the mixture quickly boiled, filtered, cooled, and stirred. Fine needles of the *arsindolinium* d-*camphorsulphonate monohydrate* separated. These were recrystallised from the aqueous alcohol (*ca.* 500 c.c.). The crop (2·95 g.) so obtained had m. p. 290°, and a 1·441% solution in pure chloroform had α + 0·97°, [*M*] + 101°. Another crystallisation gave needles, m. p. 290° (Found: C, 51·45; H, 5·0. $C_{36}H_{39}O_4Cl_2SAs,H_2O$ requires C, 51·9; H, 5·2; Cl, 11·8%); a 1·345% solution in chloroform had α + 0·96°, [*M*] + 107°. Since Holliman and Mann (*J.*, 1943, 554) have shown that the camphorsulphonate ion alone has [*M*] 111° in chloroform solution, no resolution was apparent.

Consequently, the camphorsulphonate was now recrystallised from methyl alcohol, from which it separated in fine woolly crystals; these after one and two recrystallisations had m. p. 298—302° and 302—303° respectively. The final material was still the monohydrate (Found: C, 52·3; H, 5·4; Cl, 12·0%); a 0·701% solution in chloroform had α + 0·49°, [*M*] + 105°. The chloroform solution on evaporation deposited the unchanged material, m. p. 295—296°. In view of these results the sulphonate was recovered and recrystallised 4 times from ethyl alcohol. It now separated as the *anhydrous* salt, m. p. 300° (Found: C, 53·7; H, 5·3. $C_{36}H_{39}O_4Cl_2SAs$ requires C, 53·5; H, 5·0%), and was too slightly soluble in chloroform for its rotation to be determined. It was therefore dissolved in a minimum amount of warm methyl alcohol, and treated with a concentrated methyl alcoholic solution of sodium iodide; the arsindolinium iodide which rapidly separated, when collected, washed with methyl alcohol and water, and dried, was inactive.

The spiro-*arsindolinium* l-N-1-*phenylethylphthalamate*. Solutions of the above iodide (1·957 g.) in hot aqueous alcohol (*ca.* 200 c.c.; 3 vols. water–1 vol. alcohol) and silver *l*-*N*-1-phenylethylphthalamate (1·535 g., 1 mol.) in hot 50% alcohol (120 c.c.) were mixed, briefly boiled, filtered, and cooled. As no crystals separated, the solution was concentrated first by gentle heating at *ca.* 30 mm. pressure and then by confinement in a vacuum desiccator. Magnificent rosettes of the *phthalamate monohydrate* (1·85 g., theoretical 2·53 g.), m. p. indefinite at 60—100°, separated. These were recrystallised by dissolving in warm alcohol and adding cold water until an emulsion was about to form; slow cooling and stirring gave the salt as fine crystals (1·5 g.), m. p. 145—146° on slow heating (Found: C, 59·8; H, 5·1; N, 2·3. $C_{32}H_{28}O_3NCl_2As,H_2O$ requires C, 60·1; H, 4·7; N, 2·2%). A portion when heated at 80°/0·1 mm. gave the *anhydrous* salt (Found: C, 61·8; H, 4·6. $C_{32}H_{28}O_3NCl_2As$ requires C, 61·9; H, 4·55%). A 0·652% solution of the monohydrate in alcohol was inactive. A second similar crystallisation gave the monohydrate (1·1 g.), a 0·660% solution of which in alcohol had α + 0·07°, [α] 2·7°, [*M*] + 17°, unchanged after 40 hours at room temperature; when, however, the alcohol was evaporated in a vacuum desiccator, the residual salt had m. p. 110—125°. Cold concentrated methyl-alcoholic solutions of this twice recrystallised salt and of sodium thiocyanate were mixed, whereupon the *arsindolinium thiocyanate* separated rapidly as white crystals, m. p. 223° (decomp.), which were collected and washed with water and alcohol (Found: C, 49·7; H, 3·5; N, 3·5. $C_{17}H_{14}NCl_2SAs$ requires C, 49·75; H, 3·4; N, 3·4%). A 0·713% solution in formamide was inactive.

A second similar preparation gave an initial crop of the phthalamate monohydrate which began to soften at 68° and ultimately melted at 80—115° (effer.): a 0·663% solution in alcohol had α − 0·05°. A second crystallisation gave material which shrank slightly at 120° and then melted at 137—139°; a third crystallisation gave material, m. p. 144—145° on slow heating. A 0·511% solution in alcohol was inactive. When alcoholic picric acid solution was added dropwise to a cold alcoholic solution of this last crop (*ca.* 0·3 g.), the yellow *arsindolinium picrate*, m. p. 108—112° (decomp.), was deposited (Found: N, 7·5. $C_{32}H_{16}O_7N_3Cl_2As$ requires N, 7·2%). It was collected, washed with water, and dried, but a 0·480% solution in alcohol containing 6% of acetone was inactive. The alcoholic mother-liquor from the precipitation of the picrate had α − 0·50°.

If in the above recrystallisations of the phthalamate hot water (instead of cold) was added to the hot alcoholic solution, the phthalamate separated as usual, but the m. p. [*e.g.*, 63—110° (effer.)] was now almost identical with that of the initial crop.

We are greatly indebted to Imperial Chemical Industries Ltd. for grants (D. R. L.), for conducting the therapeutic tests, and for materials.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 19th*, 1946.]

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127. *The Chemistry of the Pyrrocolines. Part V. The Action of Grignard Reagents and of Iodine on 3-Acetyl-2-phenylpyrrocoline.*

By E. T. BORROWS and D. O. HOLLAND.

When acted upon by a Grignard reagent, 3-acetyl-2-phenylpyrrocoline forms a magnesium complex which on hydrolysis yields 2-phenylpyrrocoline and a methyl ketone.

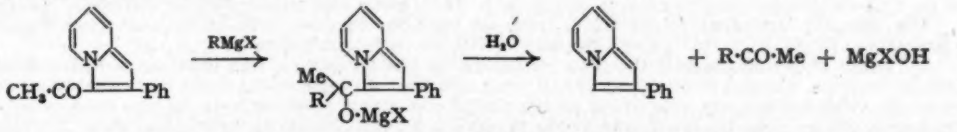
By the action of iodine, 3-acetyl-2-phenylpyrrocoline is converted into 1-iodo-3-acetyl-2-phenylpyrrocoline and 1 : 3-di-iodo-2-phenylpyrrocoline.

Two projected syntheses of 1-acetyl-2-phenylpyrrocoline failed owing to unexpected loss, at ring closure stage, of an acetyl or a hydroxethyl group resulting in the formation of 2-phenylpyrrocoline.

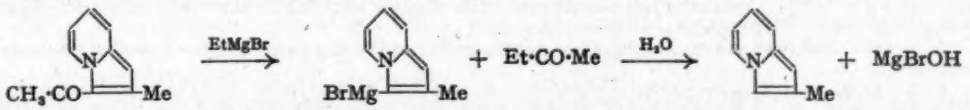
WITH the object of introducing substituents into the 3-position of the pyrrole ring in pyrrocoline, the action of various Grignard reagents on 3-acetyl-2-phenylpyrrocoline has been investigated.

Preliminary trials having shown that some acetyl compound escaped reaction when less than 1·5 mols. of the Grignard reagent were employed, this proportion was used in all subsequent experiments.

In each case the additive organo-metallic complex was isolated and failed to give a positive indication of the presence of a carbon–metal linkage (Gilman and Schultz, *J. Amer. Chem. Soc.*, 1925, **47**, 2002). On hydrolysis, the complexes yielded 2-phenylpyrrocoline and the appropriate ketone, Me·CO·R; no ketone could be isolated from the unhydrolysed complex. The reaction may therefore be formulated :



Whilst these results are in harmony with that obtained by Kondo and Osawa (*J. Pharm. Soc. Japan*, 1936, **56**, 73; *Chem. Zentr.*, 1936, **107**, ii, 2910), who showed that methyl ethyl ketone is produced when ethylmagnesium bromide reacts with 3-acetyl-2-methylpyrrocoline, they are not in agreement with the suggestion of these authors that the reaction takes the course:



Numerous attempts to isolate tertiary alcohols corresponding to (II) in the form of their acetates or benzoates were unsuccessful, and when benzoyl chloride was employed for this purpose 3-benzoyl-2-phenylpyrrocoline was obtained; this is not surprising in view of the ease of benzoylation of 2-phenylpyrrocoline (cf. Part I, *J.*, 1946, 1069).

Extension of the reaction by allowing methylmagnesium iodide and ethylmagnesium bromide to react with 3-benzoyl-2-phenylpyrrocoline resulted in the formation of metallic complexes which gave no positive indication of the presence of carbon–magnesium linkages and on hydrolysis regenerated the original 3-benzoyl compound as the principal product. It seems likely, therefore, that these metallic complexes are co-ordinate compounds of the type >C=O→MgRX. Such complexes are known to undergo intramolecular rearrangement in the presence of excess of Grignard reagent to the tertiary alcohol derivative (cf. Gilman and Jones, *J. Amer. Chem. Soc.*, 1946, **32**, 1243), and presumably this occurs to a certain extent in the above two experiments, for hydrolysis of the filtrates from the reactions gave 2-phenylpyrrocoline and the ketone (Me·CO·Ph or Et·CO·Ph).

As an alternative approach to the preparation of organo-metallic derivatives of substituted pyrrocolines, the action of iodine on 3-acetyl-2-phenylpyrrocoline was investigated. In alcoholic solution this resulted in the production of 1 : 3-*di-iodo-2-phenylpyrrocoline*, whilst in the presence of sodium acetate, to prevent hydrolysis of the acetyl group, 1-*iodo*-3-*acetyl-2-phenylpyrrocoline* was obtained.

Each of these iodo-compounds yielded α-picolinic acid *N*-oxide and benzoic acid on oxidation. Attempts to deacetylate 1-iodo-3-acetyl-2-phenylpyrrocoline, with a view to obtaining an iodo-compound suitable for the preparation of a Grignard reagent, proved unsuccessful since loss of iodine occurred before hydrolysis was complete.

An effort was made to extend these reactions to 1-acetyl-2-phenylpyrrocoline but the following two attempted syntheses of this compound were unsuccessful owing to the unexpected removal of an acetyl or a hydroxyethyl group during ring closure :

(i) 2-(2-Hydroxypropyl)pyridine combined readily with phenacyl bromide. The resultant phenacyl-2-(2-hydroxypropyl)pyridinium bromide, which was characterised as a *chloroplatinate*, on treatment with alkali underwent a retrograde aldol condensation and gave only 2-phenylpyrrocoline.

(ii) Interaction of 2-(2-ketopropyl)pyridine and phenacyl bromide gave little quaternary product, and from the crude reaction mixtures small quantities of 2-phenylpyrrocoline were isolated directly without recourse to alkaline treatment for ring closure.

Experimental.

(All m. ps. are uncorrected.)

Action of Grignard Reagents on 3-Acetyl-2-phenylpyrrocoline.—(*a*) A solution of the acetyl compound (8 g.) in ether (25 c.c.) was added dropwise to a solution of ethylmagnesium bromide (1·5 mols.) in ether

and the stirring continued for an additional 25 minutes. The resulting buff-coloured *solid* was filtered off and washed with ether (Found: N, 3·8; Br, 21·8; Mg, 6·8. $C_{18}H_{18}ONBrMg$ requires N, 3·8; Br, 21·7; Mg, 7·3%).

The combined filtrates and washings were evaporated to dryness. *iso*Propyl alcohol (10 c.c.) was added and the distillation continued; the distillate gave no precipitate with Brady's 2 : 4-dinitrophenylhydrazine reagent, but the residue, after hydrolysis with water, yielded 2-phenylpyrrocoline (0·74 g.) and a trace of methyl ethyl ketone isolated as its 2 : 4-dinitrophenylhydrazone.

The buff-coloured complex (13·44 g.) is soluble in chloroform, alcohol, pyridine, and dimethylaniline, and in the two last solvents gave a negative reaction in the Gilman and Schultz test (*loc. cit.*). On decomposition with water it yielded 2-phenylpyrrocoline (4·05 g.; 62%) and methyl ethyl ketone isolated as its 2 : 4-dinitrophenylhydrazone (1·76 g.), m. p. 114°, alone and mixed with an authentic specimen.

The complex appeared to be stable, and its alcoholic solution with picric acid gave 2-phenylpyrrocoline picrate, m. p. 161°, alone and mixed with an authentic specimen.

(*b*) When phenylmagnesium bromide (or iodide) or phenyl-lithium was used instead of ethylmagnesium bromide, parallel results (and yields) were obtained, and the reaction was not notably modified when the Grignard reagent was added to the acetyl compound or when benzene was used as solvent instead of ether. The liberated acetophenone gave a 2 : 4-dinitrophenylhydrazone, m. p. 237°, alone and mixed with an authentic specimen.

Action of Grignard Reagents on 3-Benzoyl-2-phenylpyrrocoline.—A solution of the benzoyl compound (6·65 g.) in benzene (50 c.c.) was slowly added to a solution of methylmagnesium iodide (1·5 mols.) in benzene (25 c.c.) and ether (5 c.c.), and, after 30 minutes, the yellow material (7·75 g.) was filtered off and washed with benzene. On hydrolysis with water it yielded unchanged 3-benzoyl-2-phenylpyrrocoline (4·9 g.; 74%). From the benzene filtrate, after shaking with water, there was isolated 2-phenylpyrrocoline (0·61 g.; 15%) and acetophenone (0·24 g.).

A parallel result was obtained when ethylmagnesium bromide was used instead of methylmagnesium iodide.

1 : 3-*Di-iodo-2-phenylpyrrocoline Hydriodide.*—A solution of 3-acetyl-2-phenylpyrrocoline (2·35 g.) and iodine (2·54 g.) in absolute alcohol (60 c.c.) was heated under reflux for an hour. The red needle-like product (2·8 g.) which had separated was removed by filtration and crystallised from methyl cyanide (100 c.c.); 1 : 3-*di-iodo-2-phenylpyrrocoline hydriodide* was thus obtained as iridescent bronze platelets (2·3 g.), m. p. 203° (decomp.) (Found: C, 29·3; H, 2·3; N, 2·4; I, 66·4; active H, 0·17. $C_{14}H_{9}NI_{2}.HI$ requires C, 29·3; H, 1·7; N, 2·4; I, 66·5; active H, 0·17%).

1-*Iodo-3-acetyl-2-phenylpyrrocoline.*—A solution of 3-acetyl-2-phenylpyrrocoline (0·5 g.), anhydrous sodium acetate (0·1 g.), and iodine (0·5 g.) in absolute alcohol (15 c.c.) was heated under reflux for 2 hours, concentrated, diluted with water, and extracted with ether. The 1-*iodo-3-acetyl-2-phenylpyrrocoline* separated from aqueous alcohol in yellow needles, m. p. 114—116° (0·48 g.; 63%) (Found: C, 53·3; H, 3·4; N, 3·8; I, 34·7. $C_{14}H_{12}ONI$ requires C, 53·2; H, 3·3; N, 3·9; I, 35·2%).

1 : 3-Diacetyl-2-phenylpyrrocoline, submitted to similar treatment, was recovered unchanged.

1-*Phenacyl-2-(2-hydroxypropyl)pyridinium Choroplatinate.*—A mixture of phenacyl bromide (4·4 g.) and 2-(2-hydroxypropyl)pyridine (3 g.) (*Org. Synth.*, 1943, **23**, 83) was warmed, and the vigorous reaction which followed was moderated by cooling; after 24 hours the quaternary salt had set to a non-crystallisable hard yellow glass.

A portion (0·82 g.) of this material yielded, in the usual way, 1-*phenacyl-2-(2-hydroxypropyl)pyridinium choroplatinate*, a buff-coloured powder (1·01 g.), m. p. 225° (decomp.), depressed on admixture with 1-phenacyl-2-methylpyridinium chloroplatinate of m. p. 232° (decomp.) (Found: C, 41·9; H, 4·3; N, 3·1; Pt, 21·7. $C_{32}H_{36}O_4N_2Cl_6Pt$ requires C, 41·8; H, 3·9; N, 3·05; Pt, 21·2%).

The yield of the choroplatinate was equivalent to a 90% production of the original quaternary ammonium bromide.

A solution of the quaternary ammonium bromide (1·9 g.) in water (40 c.c.) was decomposed with sodium bicarbonate, but the only crystalline product which could be isolated from the reaction mixture was 2-phenylpyrrocoline (0·5 g.), m. p. 214° (decomp.) (Found: N, 7·0. Calc.: N, 7·25%). The overall yield of 2-phenylpyrrocoline was 51%.

BATTERSEA POLYTECHNIC, LONDON, S.W.11.
GLAXO LABORATORIES, LTD., GREENFORD, MIDDLESEX.
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128. *The Chemistry of the Pyrrocolines. Part VI. The Synthesis of Pyrrocoline-2-carboxylic Acid: A New Route to Pyrrocoline.*

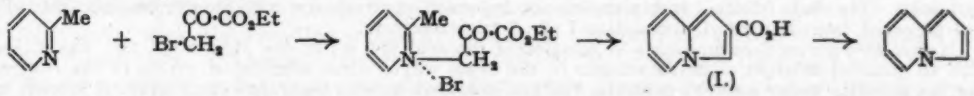
By E. T. BORROWS and D. O. HOLLAND.

Pyrrocoline-2-carboxylic acid has been synthesised in moderate yield by the action of ethyl bromopyruvate on α-picoline and shown to be identical with the product obtained by Diels and Alder by the hydrolysis and mild decarboxylation of trimethyl pyrrocoline-1 : 2 : 3-tricarboxylate.

ALTHOUGH Tschitschibabin's general method for the synthesis of pyrrocolines is very useful for the preparation of the 2-alkyl and 2-aryl derivatives (Parts I and IV, *J.*, 1946, 1069, 1083) it is of little use for the direct synthesis of pyrrocoline itself. Thus with bromoacetaldehyde and α-picoline yields of not more than 1% could be obtained, and bromoacetal and dibromoparaldehyde were even less effective (Tschitschibabin, *Ber.*, 1927, **60**, 1607). The other known

syntheses of the parent base (Part I, *loc. cit.*) also afford disappointingly low yields, the original method of Scholtz (*Ber.*, 1912, **45** 734), which is the best of these, giving approximately a 10% yield from acetic anhydride and α-picoline after hydrolysis of the 1 : 3-diacetylpyrrocoline first formed.

Since Diels and Alder (*Annalen*, 1932, **498**, 16; 1933, **505**, 103) have shown that pyrrocoline-carboxylic acids are readily decarboxylated, the possibility has been examined of using Tschitschibabin's method for the preparation of *pyrrocoline-2-carboxylic acid* (I) as an indirect synthesis of the parent base.



On mixing equimolecular amounts of ethyl bromopyruvate and α-picoline a vigorous exothermic reaction ensues accompanied by much decomposition, but in boiling alcohol the reaction proceeds smoothly and in this way it has been possible to prepare the required acid in 30% yield after ring closure with aqueous sodium hydrogen carbonate in the usual way. Attempts to isolate the corresponding ethyl ester were unsuccessful, hydrolysis apparently occurring as rapidly as ring closure.

Using bromopyruvic acid with α-picoline, only low yields of pyrrocoline-2-carboxylic acid could be obtained. On heating these two reactants in alcoholic, aqueous, or acetic acid solution there was considerable evolution of gas, and, since Sobin and Bachman (*J. Amer. Chem. Soc.*, 1935, **57**, 2458) have shown that phenylbromopyruvic acid in the presence of pyridine loses carbon dioxide, it is probable that a similar reaction takes place in this case with consequent low yields of the intermediate quaternary bromide. The best results were obtained when the reaction proceeded in alcoholic solution at room temperature.

Pyrrocoline-2-carboxylic acid thus prepared has the same m. p. [240—241° (decomp.)] as the monocarboxylic acid obtained by Diels and Alder (*loc. cit.*) by the hydrolysis and mild decarboxylation of trimethyl pyrrocoline-1 : 2 : 3-tricarboxylate, and since each on treatment with diazomethane gives the same *methyl* ester their identity is established. It would appear from this result that carboxyl groups in the 1- and the 3-position of the pyrrocoline nucleus are as labile as acetyl groups similarly substituted (Part I, *loc. cit.*).

Attempts to obtain pyrrocoline-2-carboxylic acid from 2-methylpyrrocoline by fusion with potassium hydroxide in the same way that 2-methylindole and skatole have been converted to the corresponding acids (Ciamician and Zatti, *Ber.*, 1888, **21**, 1929) were unsuccessful, the 2-methylpyrrocoline being recovered for the most part unchanged.

In the preparation of pyrrocoline-2-carboxylic acid by the method of Diels and Alder an attempt was first made to synthesis the intermediate pyrrocolinetricarboxylic ester by the procedure of Diels and Meyer (*Annalen*, 1934, **513**, 129) who recorded that it could be obtained in moderate yield by the action of pyridine on a methyl-alcoholic solution of dimethyl acetylene-dicarboxylate without cooling. However, it has been possible to isolate only a compound believed to be dimethyl 1-methoxycarbomethoxymethylpyrrocoline-2 : 3-dicarboxylate in small yield by this procedure, the compound which was stated by these workers to be formed when the reaction was carried out at 0°. The required pyrrocolinetricarboxylic ester was therefore prepared by the original method of Diels and Alder (*loc. cit.*) by the oxidation of tetramethyl pyridocoline-1 : 2 : 3 : 4-tetracarboxylate with sodium dichromate in acetic acid solution.

Since Diels and Alder have successfully converted pyrrocoline-2-carboxylic acid into the parent base by heating with calcium oxide, the extension of the general method of Tschitschibabin now described affords a convenient synthesis of pyrrocoline.

Experimental.

(All m. ps. are uncorrected.)

Ethyl bromopyruvate was prepared by a modification of the method of Ward (*J.*, 1923, **123**, 2207). To ethyl pyruvate (126·4 g.) at 50°, bromine (55 c.c.) was added with stirring at such a rate that the temperature remained at 50—60° without external heating (2·5 hours). The cooled resulting yellow liquid was diluted with chloroform (500 c.c.), water (200 c.c.) added, and the mixture stirred with calcium carbonate until effervescence ceased. The separated chloroform layer was washed with a little water and dried. After removal of the solvent the residue was distilled and the fraction, b. p. 98—105°/14 mm., collected (113 g.; 54·5% yield).

Pyrrocoline-2-carboxylic Acid.—A solution of ethyl bromopyruvate (50 g.) and α-picoline (25 c.c.) in dry alcohol (200 c.c.) was heated on the steam-bath for 4 hours, and then kept at room temperature for 3 days. The alcohol was removed under reduced pressure, the residue diluted with water, and the solution extracted with chloroform to remove coloured impurities. Sodium hydrogen carbonate was

added until effervescence ceased, and the liberated α-picoline extracted with ether. To the final brown aqueous solution excess of sodium hydrogen carbonate (20 g.) was added and the mixture heated on the steam-bath for 4 hours. Whilst still warm, the solution was acidified with dilute hydrochloric acid; *pyrrocoline-2-carboxylic acid* then separated as a grey powder (12·2 g.; 29·6% yield). A solution of the crude acid, m. p. 226° (decomp.), in hot alcohol after treatment with charcoal yielded a green solution from which the acid separated as tiny buff-coloured needles when cooled rapidly or as small cubes when cooled slowly, m. p. 240—241° (decomp.) after shrinking and darkening above 215° (Found: C, 66·8; H, 4·2; N, 9·1. $C_9H_7O_2N$ requires C, 67·1; H, 4·4; N, 8·7%).

The same compound was obtained in a less pure state in 13·8% yield by the reaction of bromopyruvic acid (Ward, *loc. cit.*) (10 g.) with α-picoline (6·0 c.c.) in dry alcohol (20 c.c.) at room temperature for 7 days. The m. p. of either specimen was not depressed on admixture with the pyrrocolinecarboxylic acid prepared from trimethyl pyrrocoline-1 : 2 : 3-tricarboxylate.

Methyl Pyrrocoline-2-carboxylate.—A solution of the acid (0·5 g.) in dry dioxan (20 c.c.) was mixed with an ethereal solution of diazomethane in the usual way. After removal of excess of the reagent and the solvents under reduced pressure, the buff-coloured residue separated from aqueous alcohol as colourless tiny platelets of the *ester*, m. p. 97—99° after sintering at 90° (Found: C, 68·2; H, 5·3; N, 7·9. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·1; N, 8·0%).

Reaction of Dimethyl Acetylenedicarboxylate with Pyridine in Methyl-alcoholic Solution.—To a solution of dimethyl acetylenedicarboxylate (Moureu and Bongrand, *Ann. Chim. Phys.*, 1920, **14**, 11) (16·5 c.c.) in dry methyl alcohol (45 c.c.), dry pyridine (9 c.c.) was added in four portions. A vigorous reaction set in at first but moderated towards the end of the addition. No solid separated from the resulting red-brown solution after 2 days in the ice-chest. On dilution with water (75 c.c.) a red-brown oil was deposited from which a mass of crystals separated after 1 day. The crude solid (1·27 g.) after being washed with a little methyl alcohol was recrystallised from this solvent; the suspected dimethyl 1-methoxycarbomethoxymethylpyrrocoline-2 : 3-dicarboxylate was thus obtained as colourless needles, m. p. 138—139·5° (*lit.*, m. p. 142—143°), largely depressed on admixture with the trimethyl ester prepared by the method of Diels and Alder (Found: C, 57·2; H, 5·3; N, 4·4. Calc. for $C_{14}H_{17}O_7N$: C, 57·3; H, 5·1; N, 4·2%).

The above suspected methoxy-ester reacted readily with nitric acid in acetic acid solution under the conditions described by Diels and Meyer (*loc. cit.*) to give dimethyl 1-nitropyrrocoline-2 : 3-dicarboxylate, m. p. 160—161° (*lit.*, m. p. 165°) (Found: C, 52·3; H, 3·8; N, 10·4. Calc. for $C_{12}H_{10}O_6N_2$: C, 51·8; H, 3·6; N, 10·1%). After similar treatment trimethyl pyrrocoline-1 : 2 : 3-tricarboxylate was recovered unchanged.

The authors of this and the preceding paper wish to thank Dr. J. Kenyon for continued encouragement in this work.

BATTERSEA POLYTECHNIC, LONDON, S.W.11.
GLAXO LABORATORIES, LTD., GREENFORD, MIDDLESEX. [*Received, August 21st*, 1946.]

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129. *Studies on Phosphorylation. Part III. Further Observations on the Reaction of Phosphites with Polyhalogen Compounds in Presence of Bases and its Application to the Phosphorylation of Alcohols.*

By F. R. ATHERTON and A. R. TODD.

The reaction between dialkyl phosphites and carbon tetrachloride in presence of bases described in Part II of this series (Atherton, Openshaw, and Todd, *J.*, 1945, 660) has been further studied using a variety of polyhalogen compounds. In general the reactivity of halogen compounds is decreased by introduction of fluorine and increased by bromine or iodine, and the reaction can also be used with diphenyl phosphite. In using the reaction as a preparative phosphorylation procedure, trichlorobromomethane appears to be the reagent of choice. A mixture of this substance with a phosphite will phosphorylate even aromatic amines directly, and in presence of a suitable tertiary base will phosphorylate ethyl alcohol.

The mechanism of the reaction is considered in the light of these further studies, and it is concluded that contrary to the view expressed earlier the main pathway of reaction involves intermediate formation of a halogenophosphonate which then acts as a phosphorylating agent.

IN Part II (*loc. cit.*) a reaction between dialkyl phosphites with carbon tetrachloride in presence of bases was described, which could be utilised for the phosphorylation of amines; the overall reaction in the case of a strong primary or secondary base could be represented by the equation

$$(RO)_2\overset{\overset{O}{\|}}{P}\text{—}H + CCl_4 + 2R'R''NH \longrightarrow (RO)_2\overset{\overset{O}{\|}}{P}\text{—}NR'R'' + R'R''NH,HCl + CHCl_3$$

In the case of weakly basic amines (*e.g.*, aniline) addition of a strong tertiary base was necessary to induce reaction. In the same paper it was noted that this unusual reaction was not confined to carbon tetrachloride for, although chloroform and *s*-tetrachloroethane could not replace it, pentachloroethane and hexachloroethane reacted smoothly. The present communication

describes some further studies designed to test the general applicability of the reaction, to find the most suitable polyhalogen compound for general use in phosphorylation, and to gain further insight into its mechanism.

As a preliminary a number of further polyhalogenated hydrocarbons containing chlorine, or both chlorine and fluorine, were examined as substitutes for carbon tetrachloride. The results of a qualitative survey are given in the following table; the production of base hydrohalide on mixing dibenzyl phosphite, halogen compound, and ammonia or *cyclo*hexylamine was taken as a criterion, controls being carried out in the absence of phosphite. Some of the reactions listed in the table were studied in a more quantitative fashion, the amino-phosphonate being isolated from the resulting mixture; details of two such experiments are given in the Experimental part. In general, reactivity in chlorofluoro-compounds decreased with increasing fluorine content, and in each case chloride ions were liberated with at most only traces of fluoride. The fact that tetrachloro-1 : 2-difluoroethane can take the place of carbon tetrachloride suggests that the failure of *s*-tetrachloroethane to do so may be due simply to preferential dehydrohalogenation in presence of bases.

Reactivity of polyhalogen compounds with cyclo*hexylamine in presence of dibenzyl phosphite.*

Compound.	Reaction.	Compound.	Reaction.
$CH_3 \cdot CCl_3$	−	$CHCl_2 \cdot CF_2Cl$	Reacts with base alone
$CH_2Cl \cdot CCl_3$	+ [1]	$CFCl_2 \cdot CFCl_2$	+ [1]
$CF_2Cl \cdot CCl_3$	+ [1]	$CCl_2:CCl_2$	−
$(p\text{-}Cl \cdot C_6H_4)_2CH \cdot CCl_3$	−	$CHCl:CCl_2$	−
$CH_2Cl \cdot CHCl_2$	− [2]	$CCl_3 \cdot CCl_2 \cdot CCl_3$	+
$CH_2Cl \cdot CFCl_2$	+ [1]	$CCl_3 \cdot CCl_2 \cdot CCl_2 \cdot CCl_3$	+
$CH_2Cl \cdot CF_2Cl$	−	$CCl_2:CCl \cdot CCl_3$	+
$CF_2Cl \cdot CFCl_2$	+ [1]	$CCl_2:CCl \cdot CCl:CCl_2$	−

[1] No reaction when ammonia was substituted for *cyclo*hexylamine.
[2] Slow reaction occurs with base alone.

None of the active compounds listed in the table showed any practical advantages over carbon tetrachloride as a reagent, and attention was next directed to the use of accessible bromo- and iodo-compounds. Carbon tetrabromide reacted vigorously with dibenzyl phosphite in presence even of such weak bases as aniline, giving the corresponding substituted amino-phosphonates in excellent yield. A noteworthy feature of this reagent is that the bromoform produced reacts further being itself converted into methylene bromide, so that 1 mol. of carbon tetrabromide will effect complete phosphorylation of 2 mols. of an amine. Iodoform behaved very like bromoform, although the reaction products were contaminated with iodine, and dichlorobromomethane could also be used successfully. The very high degree of reactivity shown by carbon tetrabromide was also observed in tetrachloro-1 : 2-dibromoethane, which was converted on reaction into a mixture of tetrachloroethylene and trichlorobromoethylene.

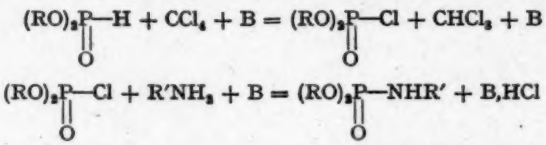
From a practical standpoint the use of carbon tetrabromide in phosphorylating compounds by the reaction under discussion has the disadvantage that the methylene bromide produced has rather a high boiling point. It seemed, therefore, that the reagent of choice might well be trichlorobromomethane, which would be converted into chloroform during reaction. Difficulty was at first encountered in preparing this substance in bulk, but a convenient method was found in the vapour-phase bromination of chloroform. Our expectations as to its usefulness were entirely fulfilled, and a mixture of it with dibenzyl phosphite was found to phosphorylate weak bases such as aniline and *N*-methylaniline directly. Moreover, in presence of a tertiary base the same mixture successfully phosphorylated ethyl alcohol. Trichlorobromomethane is considered to be the best polyhalogen compound for general use in the phosphorylation of amines and alcohols by this method; examples of its application are given in the Experimental section. A point of practical interest is that not only dialkyl phosphites but also diphenyl phosphite can be used in the reaction with polyhalogen compounds and bases.

In Part II (*loc. cit.*) the mechanism of the phosphorylation of amines by carbon tetrachloride and dialkyl phosphites in the presence of strong bases was discussed, and it was suggested that the reaction proceeded in two stages with intermediate formation of a trichloromethylphosphonate as indicated below :

1. $(RO)_2\overset{\overset{O}{\|}}{P}\text{—}H + CCl_4 + B = (RO)_2\overset{\overset{O}{\|}}{P}\text{—}CCl_3 + B,HCl$

2. $(RO)_2\overset{\overset{O}{\|}}{P}\text{—}CCl_3 + R'NH_2 = (RO)_2\overset{\overset{O}{\|}}{P}\text{—}NHR' + CHCl_3$

Attempts to demonstrate the reality of this scheme by interruption at stage 1 failed as the intermediate product appeared too unstable to be isolated. As the above scheme bore an analogy to certain other reactions of carbon tetrachloride, and as we failed to phosphorylate alcohols by using a mixture of carbon tetrachloride, dialkyl phosphite, and a strong tertiary base, it was at the time preferred to the alternative mechanism summarised in equations 3 and 4 in which the intermediately produced phosphorylating agent is a dialkyl chlorophosphonate.



These opinions must now be revised in the light of the results obtained in our more recent work. Whether reaction according to equation 1 or 3 occurs will depend on whether carbon tetrachloride reacts effectively as $CCl_3^+Cl^-$ or $CCl_3^-Cl^+$, the anion being eliminated with a proton from the phosphite in the formation of the phosphorylating agent. Bromine being less electronegative than chlorine, its substitution for chlorine in the carbon tetrachloride molecule should favour reaction according to equation 3 The fact that introduction of bromine in this way greatly increases activity, so that even weak bases can be phosphorylated without adding a tertiary base, is very much in favour of the mechanism indicated in equations 3 and 4. The phosphorylation of ethyl alcohol using trichlorobromomethane is also evidence pointing in the same direction. Very strong evidence for this mechanism is also to be found in the observation that both trichlorobromomethane and carbon tetrachloride react with dibenzyl phosphite in presence of sodium or potassium hydroxide to give tetrabenzyl pyrophosphate; this compound is known to be formed by the action of potassium hydroxide on dibenzyl chlorophosphonate (Deutsch and Fernö, *Nature*, 1945, **156**, 604) and it is difficult to account for its formation on the basis of an initial reaction according to equation 1.

The acceptance of the mechanism given in equations 3 and 4 involves the assumption that the active polyhalogen compounds contain " positive " halogen. This may seem surprising in the case of carbon tetrachloride, but it is not without analogy among the other reactions of this compound. Thus it causes oxidation of sodium thioalkoxides, NaSR, to disulphides (Backer and Stedehouder, *Rec. Trav. chim.*, 1933, **52**, 437) in the same way as other compounds containing " positive " halogen (Kohler and Potter, *J. Amer. Chem. Soc.*, 1936, **58**, 2166); chloroform and ethylene and methylene halides on the other hand react normally with sodium thioalkoxides, the halogen atoms being replaced by alkylthio-groups (Stutz and Shriner, *J. Amer. Chem. Soc.*, 1933, **55**, 1242). While we consider that our evidence to date is in favour of a mechanism involving intermediate formation of a halogeno-phosphonate which then acts as a phosphorylating agent, the possibility that some reaction according to equations 1 and 2 may also occur, especially with carbon tetrachloride, cannot be excluded. The failure to phosphorylate alcohols using carbon tetrachloride, recorded in Part II (*loc. cit.*), does not give any strong support to the existence of a trichloromethylphosphonate intermediate, for it is now realised that dibenzyl chlorophosphonate is very unstable in the presence of strong tertiary bases such as *N*-methylmorpholine which were used to induce reaction.

Experimental.

Attention is drawn to the following *errata* in Part I (Atherton, Openshaw, and Todd, *J.*, 1945, 382). In the preparation of dibenzyl hydrogen phosphite, *for* " phosphorus trichloride (147·5 g.; 1 mol.)" *read* " phosphorus trichloride (137·5 g.; 1 mol.) ". Further work has shown that the m. p. of dibenzyl phosphite can be raised by purification to 17°. In the preparation of dibenzyl chlorophosphonate, *for* " 200 c.c. of 1·4N " *read* " 220 c.c. of 1·4N ").

Reactions of Chloro- and Chlorofluoro-compounds with cyclo*Hexylamine and Dibenzyl Phosphite.*—(a) as-*Tetrachloroethane.* *cyclo*Hexylamine (8 c.c.) was added to a solution of dibenzyl phosphite (5·24 g.) and *as*-tetrachloroethane (10 c.c.) in methylene chloride (25 c.c.) and the mixture set aside overnight. After being washed with water and dilute acid the dried reaction solution was evaporated to dryness. Recrystallisation from hexane gave dibenzyl *cyclo*hexylaminophosphonate (4 g.; 56%), m. p. and mixed m. p. 79—80°.

(b) *Trichloro*-1 : 1 : 2-*trifluoroethane.* A mixture of dibenzyl phosphite (2·62 g.), trichloro-1 : 1 : 2-trifluoroethane (15 c.c.), and *cyclo*hexylamine (4 c.c.) was kept at room temperature during 18 hours with occasional shaking. Worked up in the usual way the product (2·3 g.; 64%) after several recrystallisations from hexane had m. p. 74—76°. The m. p. was not depressed by admixture with authentic dibenzyl *cyclo*hexylaminophosphonate (m. p. 79—80°), but it did not seem to be affected by further recrystallisation; the nature of the impurity responsible was not ascertained. Similar difficulty was

encountered in purifying the products when other fluorine-containing compounds were employed in the reaction.

Reaction of Dibenzyl Phosphite with Ammonia and cyclo*Hexylamine in Presence of Bromo- and Iodo-compounds.*—The reactions were carried out at room temperature in the usual manner (reaction time, 30 minutes) and the products isolated as described above. For convenience the results are tabulated. In each case the amount of dibenzyl phosphite used was 0·01 mole and methylene chloride was employed as a diluent.

Amount of diluent (c.c.).	Halogen compound.	Quantity used (moles).	Yield of dibenzyl amino-phosphonate (%).	Yield of dibenzyl *cyclo*hexyl-aminophosphonate (%).
20	CHI_3	0·01	81	83
20	$CHBr_3$	0·012	90	80
20	$CHBrCl_2$	0·015	43 [1]	87
25	$CCl_2Br{\cdot}CCl_2Br$	0·01	91	90
50	CBr_4	0·005	—	84

[1] Low yield due to incomplete reaction in 30 minutes.

Reaction of Various Phosphites with Aniline in Presence of Carbon Tetrabromide.—Carbon tetrabromide was added to a mixture of the dialkyl or dibenzyl phosphite and aniline at room temperature and the product worked up next day. Yields of anilinophosphonate: from dibenzyl phosphite, 91%; diethyl phosphite, 88%; di*iso*propyl phosphite, 40%.

Isolation of Halogenated Reaction Products.—The method employed was to pass a slow stream of gaseous ammonia for several hours through an ethereal solution containing equimolar quantities of di*iso*propyl phosphite and the appropriate polyhalogen compound. The ammonium halide was filtered off, the ether removed, and the residue steam distilled under reduced pressure. The product was separated from the distillate and fractionated. Treated in this way hexachloroethane gave tetrachloroethylene (70%, b. p. 120—121°), iodoform gave methylene iodide (80%, b. p. 90°/42 mm.), bromoform gave methylene bromide (59%, b. p. 96—97°), and tetrachloro-1 : 2-dibromoethane gave a mixture of tetrachloroethylene (54%, b. p. 121°) and trichlorobromoethylene (6·5%, b. p. 145—147°).

Trichlorobromoethane.—The vapour from a refluxing mixture of dry chloroform (400 c.c.) and bromine (320 g.) was carried by a stream of nitrogen through a vertical silica tube heated to 250° and then through an efficient condenser, the condensate being returned to the flask containing the refluxing mixture. Hydrogen bromide was rapidly evolved and when, after 3 hours, the bromine colour had disappeared, the mixture was allowed to cool, washed with dilute sodium carbonate, and dried (Na_2SO_4). Fractionation using a 20 cm. Fenske coloumn gave trichlorobromomethane, b. p. 104° (yield: 294 g.; 74%); the distillation residue which solidified on cooling consisted almost entirely of hexachloroethane.

Direct Phosphorylation of Aniline and other Weak Bases by Means of Trichlorobromomethane and a Phosphite.—A mixture of the dibenzyl or other phosphite with trichlorobromomethane, diluted with an inert solvent (benzene or ethyl acetate), was allowed to react with the appropriate amine at room temperature. After 18 hours the products were worked up in the usual way. In this way were prepared the known diethyl anilinophosphonate (yield, 88%), di*iso*propyl anilinophosphonate (yield, 62%) and dibenzyl anilinophosphonate (yield, 92%) as well as the following: *dibenzyl β-naphthylaminophosphonate*, colourless prisms, m. p. 75·5—76·5°, from *cyclo*hexane–ether (Found: C, 71·1; H, 5·2; N, 3·5. $C_{24}H_{22}O_3NP$ requires C, 71·5; H, 5·4; N, 3·5%) (yield, 93%); *dibenzyl p-toluidinophosphonate*, colourless prisms, m. p. 89·5—90·5°, from light petroleum (Found: C, 68·0; H, 6·0; N, 3·8. $C_{21}H_{22}O_3NP$ requires C, 68·5; H, 6·0; N. 3·8%) (yield, 89%); *dibenzyl N-methylanilinophosphonate*, colourless prisms, m. p. 86—87°, from light petroleum (Found: C, 68·0; H, 6·0; N, 3·7. $C_{21}H_{22}O_3NP$ requires C, 68·5; H, 6·0; N, 3·8%) (yield, 64%).

Barium Ethyl Phosphate.—A mixture of dibenzyl phosphite (5·24 g.), ethyl alcohol (3 c.c.), 2 : 6-lutidine (5 c.c.), trichlorobromomethane (5 c.c.), and dry ether (25 c.c.) was set aside at room temperature for 2½ hours. The oil obtained by working up in the usual manner was evaporated with water to remove traces of lachrymatory material, dissolved in alcohol, and boiled for a few minutes with charcoal. The filtered solution (100 c.c.) was hydrogenated at atmospheric pressure using palladium oxide catalyst. When absorption of hydrogen was complete (10 minutes; 750 c.c.) the mixture was filtered and neutralised to phenolphthalein with barium hydroxide, and the alcohol removed under reduced pressure. The residue was dissolved in water, and the solution filtered, concentrated, and brought to crystallisation by adding alcohol. Barium ethyl phosphate separated as its crystalline hydrate, and was converted to the anhydrous salt (2·7 g.; 51%) by drying at 100° (Found: Ba, 52·1. Calc. for $C_2H_5O_4PBa$: Ba, 52·6%).

Diphenyl Aminophosphonate.—Ammonia was passed through a solution of diphenyl phosphite (2·34 g.) in carbon tetrachloride (25 c.c.) for 15 minutes. The product (2·05 g.; 82%), recrystallised from chloroform–light petroleum, had m. p. 149—150°, undepressed in admixture with authentic diphenyl aminophosphonate (m. p. 149—150°).

Tetrabenzyl Pyrophosphate.—A mixture of dibenzyl phosphite (26·2 g.), carbon tetrachloride (30 c.c.), and aqueous potassium hydroxide (250 c.c. of N) was stirred at room temperature for 9½ hours. The phases were then separated, the aqueous phase being washed with carbon tetrachloride. The combined carbon tetrachloride solutions were washed with water, dried (Na_2SO_4), and evaporated, and the residual oil was dissolved in a small amount of ether (*ca.* 50 c.c.) and *cyclo*hexane added until slightly turbid. On standing, tetrabenzyl pyrophosphate separated in colourless needles (16·5 g.; 61%), m. p. 60—61° undepressed by a sample (m. p. 60—61°) prepared according to Deutsch and Fernö (*loc. cit.*). From the aqueous phase, acidification and recrystallisation gave dibenzyl phosphate (2·6 g.; 9%), m. p. and mixed m. p. 78—79°, while fractionation of the distillate from the isolation of the tetrabenzyl pyrophosphate gave chloroform (5 g.; 42%).

A similar experiment was carried out using trichlorobromomethane in place of carbon tetrachloride.

In this case difficulty was experienced in crystallising the oily tetrabenzyl pyrophosphate, and it was therefore identified by treatment with ammonia; it then yielded the expected mixture of dibenzyl aminophosphonate and dibenzyl phosphate.

It may be observed in passing that tetrabenzyl pyrophosphate is a satisfactory phosphorylating agent—with ammonia it gave in a trial experiment dibenzyl aminophosphonate (93%) and dibenzyl phosphate (90%)—and the fact that it can readily be prepared and stored in a crystalline condition gives it certain advantages as a reagent.

We are grateful to Roche Products Ltd. for a scholarship held by one of us (F. R. A.) and to Imperial Chemical Industries (General Chemicals) Ltd. for the gift of a number of polyhalogen compounds used in the investigations.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 21st,* 1946.]

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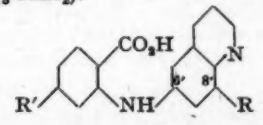
130. *Attempts to find New Antimalarials. Part XXV. Some Derivatives of 3 : 4 : 2′ : 3′-Pyridoacridine substituted in the 2-Position.*

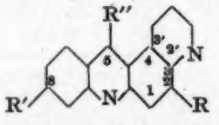
By WILLIAM C. HUTCHISON and WILLIAM O. KERMACK.

A number of derivatives of 3 : 4 : 2′ : 3′-pyridoacridine have been prepared containing a chlorine atom in position 2, with and without a chlorine atom simultaneously present in position 8. A further series of derivatives contain a methyl group in position 2 and a chlorine atom in position 8. Of the compounds containing a γ-diethylaminopropylamino-side chain in position 5, the 2-chloro-derivative possessed considerable antimalarial activity, whilst the 2 : 8-dichloro-derivative was markedly active.

THE preparation of certain 3 : 4 : 2′ : 3′-pyridoacridine derivatives possessing activity against *P. gallinaceum* in chicks has been described (Dobson and Kermack, *J.*, 1946, 150), and the chemotherapeutic effect was found to be intensified by a chlorine atom in position 8 of the acridine nucleus. It appeared of interest to ascertain the effect of a chlorine atom at position 2, which in the unsubstituted acridine nucleus is equivalent to position 8. To this end *8-chloro-6-aminoquinoline* was condensed with *o*-chlorobenzoic acid to yield 8′-chloro-6′-quinolylanthranilic acid (I, R = Cl; R′ = H), purified as its *ethyl* ester. This acid was cyclised by treatment with phosphoryl chloride to *2 : 5-dichloro-3 : 4 : 2′ : 3′-pyridoacridine* (II, R = R″ = Cl; R′ = H) from which *2-chloro-3 : 4 : 2′ : 3′-pyridoacridone* (II, R = Cl; R′ = H; R″ = OH) was prepared by heating with dilute hydrochloric acid. The 2 : 5-dichloro-3 : 4 : 2′ : 3′-pyridoacridine on treatment with γ-diethylaminopropylamine in dry phenol at 100° yielded *2-chloro-5-(γ-diethylaminopropylamino)-3 : 4 : 2′ : 3′-pyridoacridine* (II, R = Cl; R′ = H; R″ = NH·[CH$_2$]$_3$·NEt$_2$).

(I.)

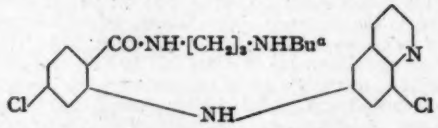




(II.)

The effect of a second chlorine atom in this base was investigated by carrying out a similar series of reactions in which the *o*-chlorobenzoic acid was replaced by 2 : 4-dichlorobenzoic acid. This yielded successively *4 : 8′-dichloro-6′-quinolylanthranilic acid* (I, R = R′ = Cl), 2 : 5 : 8-trichloro-3 : 4 : 2′ : 3′-pyridoacridine (II, R = R′ = R″ = Cl), and *2 : 8-dichloro-5-(γ-diethylaminopropylamino)-3 : 4 : 2′ : 3′-pyridoacridine* (II, R = R′ = Cl; R″ = NH·[CH$_2$]$_3$·NEt$_2$). *2 : 8-Dichloro-5-(γ-butylaminopropylamino)-3 : 4 : 2′ : 3′-pyridoacridine* (II, R = R′ = Cl; R″ = NH·[CH$_2$]$_3$·NHBu) was obtained from 2 : 5 : 8-trichloro-3 : 4 : 2′ : 3′-pyridoacridine and γ-butylaminopropylamine.

2 : 8-Dichloro-5-(γ-butylaminopropylamino)-3 : 4 : 2′ : 3′-pyridoacridine was also prepared in poor yield by refluxing 4 : 8′-dichloro-6′-quinolylanthranil-(γ-butylaminopropyl)amide (III) (from 4 : 8′-dichloro-6′-quinolylanthranilic acid chloride and γ-butylaminopropylamine)



(III.)

with phosphoryl chloride. This method has previously been used by Drosdov (*J. Gen. Chem. Russia*, 1938, **8**, 1192) in preparing compounds of the mepacrine type.

When 6-amino-8-methylquinoline was condensed with 2 : 4-dichlorobenzoic acid, 4-chloro-(8′-methyl-6′-quinolyl)anthranilic acid (I, R = Me; R′ = Cl) was obtained and purified as its *ethyl* ester, but all attempts to convert this acid directly with phosphoryl chloride into 5 : 8-*dichloro-2-methyl*-3 : 4 : 2′ : 3′-*pyridoacridine* (II, R = Me; R′ = R″ = Cl) failed to give a satisfactory product. Most of the material obtained after treatment with dilute sodium hydroxide solution was insoluble in benzene, and the small quantity which did crystallise from benzene gave unsatisfactory analytical results. A two-stage process, however, was successful; the acid was cyclised to 8-*chloro-2-methyl*-3 : 4 : 2′ : 3′-*pyridoacridone* (II, R = Me; R′ = Cl; R″ = OH) with warm concentrated sulphuric acid, and, when this pyridoacridone was refluxed with phosphoryl chloride containing phosphorus pentachloride, 5 : 8-dichloro-2-methyl-3 : 4 : 2′ : 3′-pyridoacridine was obtained. Condensation of this compound with γ-diethylaminopropylamine in phenol yielded the expected 8-*chloro-2-methyl*-5-(γ-*diethylaminopropylamino*)-3 : 4 : 2′ : 3′-*pyridoacridine* (II, R = Me; R′ = Cl; R″ = NH·[CH_2]$_3$·NEt_2).

Antimalarial tests were carried out on *P. gallinaceum* infections of chicks in the Biological Laboratories of Imperial Chemical Industries Ltd. Full details of the biological tests will be published elsewhere. The activities of the compounds prepared are shown in the Table, the activity at various doses being indicated as negative (−), slight (+), or marked (++). For comparison the activities of mepacrine and of 8-chloro-5-(γ-diethylaminopropylamino)-3 : 4 : 2′ : 3′-pyridoacridine (3652) prepared by Dobson and Kermack (*loc. cit.*) are also shown.

Reference No.	Formula of base.	Dose, mg./kg.	Activity.
—	Mepacrine	40	++
		20	+
3652	II, R = H; R′ = Cl; R″ = NH·[CH_2]$_3$·NEt_2	120	++
		80	+
		40	−
4774	II, R = Cl; R′ = H; R″ = NH·[CH_2]$_3$·NEt_2	120	++
		80	++
		40	−
4602	II, R = R′ = Cl; R″ = NH·[CH_2]$_3$·NEt_2	120	++
		80	++
		40	++
		20	+
5070	II, R = R′ = Cl; R″ = NH·[CH_2]$_3$·NHBu	160	++
		120	++
		80	++
		40	±
5754	II, R = Me; R′ = Cl; R″ = NH·[CH_2]$_3$·NEt_2	80	++
		40	+

It will be seen that the 2-chloro-compound (4774) is at least as active as, if not slightly more active than, the 8-chloro-isomer (3652), and that the 2 : 8-dichloro-compound (4602) is more potent than either of these monochloro-derivatives. The γ-butylaminopropylamino-side chain, which was better than γ-diethylaminopropylamino- in the 8-chloro-series, did not show a corresponding superiority in the 2 : 8-dichloro-series. The methyl group in position 2 appears to increase slightly the antimalarial activity of the 8-chloro-compound, but the toxicity seems also to be considerably raised.

Experimental.

8′-*Chloro-6′-quinolylanthranilic Acid.*—8-Chloro-6-aminoquinoline * (21·5 g., m. p. 154°, obtained by reduction of 8-chloro-6-nitroquinoline by West's method (*J.*, 1925, **127**, 494)), potassium *o*-chlorobenzoate (24·5 g.), copper bronze (0·1 g.), and amyl alcohol (40 c.c.) were refluxed for 6 hours in an oil-bath at 150°. The amyl alcohol was removed by filtration, and the residue well washed with acetone and extracted with a large volume of hot dilute ammonia; the filtrate yielded, on acidification with acetic acid, a brown-yellow precipitate of 8′-chloro-6′-quinolylanthranilic acid in relatively small yield. A further quantity was obtained by extracting the residue with 2N-hydrochloric acid on the boiling water-bath and filtering hot. The hydrochloride of the acid separated on cooling; it was suspended in water and made alkaline with ammonia. The yellow residue insoluble in dilute hydrochloric acid evidently consisted of the relatively insoluble hydrochloride of the acid, for on treatment with ammonia it yielded crude 8′-chloro-6′-quinolylanthranilic acid. 8′-Chloro-6′-quinolylanthranilic acid crystallised from alcohol as grey-brown needles, m. p. 256°. Yield, 20·5 g.

For analysis, the ethyl ester was prepared by refluxing the acid (1 g.) with ethyl alcohol (10 c.c.) and

* This *compound* had previously been prepared by Dr. F. H. S. Curd (private communication) who recrystallised it from ethyl acetate–light petroleum (charcoal); it then had m. p. 156—157° (Found : C, 60·55; H, 4·15; Cl, 20·15. $C_9H_7N_2Cl$ requires C, 60·5; H, 3·9; Cl, 19·9%).

concentrated sulphuric acid (3 c.c.) for 2 hours. The cooled solution was poured into ice–water, filtered, the filtrate made alkaline with ammonia, and the yellow oily precipitate extracted with ether. The residue after removal of the ether solidified on treatment with warm dilute aqueous sodium hydrogen carbonate and cooling. *Ethyl 8′-chloro-6′-quinolylanthranilate* crystallised from alcohol as white needles, m. p. 118° (Found: C, 66·25; H, 4·5; N, 8·6. $C_{18}H_{15}O_2N_2Cl$ requires C, 66·2; H, 4·6; N, 8·6%).

2 : 5-*Dichloro*-3 : 4 : 2′ : 3′-*pyridoacridine*.—8′-Chloro-6′-quinolylanthranilic acid (6 g.) and phosphoryl chloride (30 c.c.) were refluxed for 6 hours in an oil-bath at 150°. The excess of phosphoryl chloride was removed by distillation under reduced pressure, and the residue triturated with 2N-sodium hydroxide and ice. The washed residue was dried in a desiccator and extracted in the presence of a pellet of potassium hydroxide with benzene which had been dried over sodium. The *pyridoacridine* crystallised easily from dry benzene as yellow needles, m. p. 208°. Yield, 4·7 g. (Found: C, 64·75; H, 2·6; N, 9·6; Cl, 23·5. $C_{16}H_8N_2Cl_2$ requires C, 64·2; H, 2·7; N, 9·4; Cl, 23·7%).

2-*Chloro*-3 : 4 : 2′ : 3′-*pyridoacridone*.—2 : 5-Dichloro-3 : 4 : 2′ : 3′-pyridoacridine was heated for 2 hours at 100° with N-hydrochloric acid. The bright yellow compound formed, evidently the hydrochloride (m. p. >400°), changed to light yellowish-brown on treatment with ammonia, and the filtrate gave a reaction for chloride ions. The *pyridoacridone* crystallised from alcohol as yellow needles, m. p. over 400° (Found: C, 67·4; H, 3·6; N, 9·9. $C_{16}H_9ON_2Cl,\frac{1}{2}H_2O$ requires C, 67·4; H, 3·3; N, 9·8%).

2-Chloro-3 : 4 : 2′ : 3′-pyridoacridone was also produced by refluxing 2 : 5-dichloro-3 : 4 : 2′ : 3′-pyridoacridine with ethyl alcohol, even though the latter contained less than 1% of water (cf. Dobson and Kermack, *loc. cit.*).

2-*Chloro*-5-(γ-*diethylaminopropylamino*)-3 : 4 : 2′ : 3′-*pyridoacridine*.—2 : 5-Dichloro-3 : 4 : 2′ : 3′-pyridoacridine (1 g.) and γ-diethylaminopropylamine (1 g.) were heated in dry molten phenol at 100° for 2 hours (cf. Dobson and Kermack, *loc. cit.*). The cooled phenol mixture was poured into 2N-sodium hydroxide and the yellow oily precipitate extracted with ether. The base was purified by shaking the ethereal extract with 5% acetic acid, reprecipitating with ammonia, and re-extracting with ether. This ethereal extract was dried (K_2CO_3) and the ether distilled off. The residual brownish-red oily solid was heated at 100° in a vacuum to remove excess of γ-diethylaminopropylamine and the sticky solid which remained dissolved in hot dry ligroin. 2-*Chloro*-5-(γ-*diethylaminopropylamino*)-3 : 4 : 2′ : 3′-*pyridoacridine*, which separated from the filtered solution on cooling, crystallised after 2 days at room temperature. Yield, 0·7 g., m. p. 109°. Twice recrystallised from dry ligroin, it had m. p. 115° (Found: C, 69·9; H, 6·4; N, 13·95. $C_{23}H_{21}N_4Cl$ requires C, 70·3; H, 6·4; N, 14·3%).

4 : 8′-*Dichloro*-6′-*quinolylanthranilic Acid*.—8-Chloro-6-aminoquinoline (12 g.), potassium 2 : 4-dichlorobenzoate (15·3 g.), amyl alcohol (16·7 c.c.), and copper bronze (0·1 g.) were heated under reflux for 6 hours in an oil-bath at 150°. The product was worked up exactly as described for 8′-chloro-6′-quinolylanthranilic acid. Yield, 12·3 g. The *acid* crystallised from alcohol as white needles, m. p. 300°. This acid like the other quinolylanthranilic acids was difficult to purify, and even a sample recrystallised several times showed a trace of ash [Found: C, 56·6; H, 3·35; N, 8·65; ash, 0·5 (approx.). $C_{16}H_{10}O_2N_2Cl_2,\frac{1}{2}H_2O$ requires C, 56·1; H, 3·2; N, 8·2%].

2 : 5 : 8-*Trichloro*-3 : 4 : 2′ : 3′-*pyridoacridine*.—4 : 8′-Dichloro-6′-quinolylanthranilic acid (6 g.) was refluxed with phosphoryl chloride (30 c.c.) as described above for 8′-chloro-6′-quinolylanthranilic acid. Yield, 3 g. The product even after repeated recrystallisations from dry benzene (brown-yellow needles, m. p. 286°) was not analytically pure, but was used for condensation with γ-diethylaminopropylamine and γ-butylaminopropylamine. This failure to obtain 2 : 5 : 8-trichloro-3 : 4 : 2′ : 3′-pyridoacridine pure was an example in an acute form of the general difficulty of purification encountered with almost all 5-chloropyridoacridines.

The residue insoluble in benzene appeared to consist largely of 2 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridone, for when 5 g. of it were refluxed with phosphoryl chloride (25 c.c.) containing phosphorus pentachloride (3·3 g.) for 6 hours in an oil-bath at 150° and the product worked up as described above, some 2 : 5 : 8-trichloro-3 : 4 : 2′ : 3′-pyridoacridine was obtained. Yield, 1 g.; m. p. 268—269°.

2 : 8-*Dichloro*-5-(γ-*diethylaminopropylamino*)-3 : 4 : 2′ : 3′-*pyridoacridine*.—2 : 5 : 8-Trichloro-3 : 4 : 2′ : 3′-pyridoacridine (1 g.) and γ-diethylaminopropylamine (1 g.) were heated in dry molten phenol (10 g.) for 2 hours at 100°. The cooled phenol mixture was poured into 2N-sodium hydroxide (30 c.c.) and the brown precipitate filtered off, washed, extracted with 5% acetic acid, filtered, and the filtrate basified with ammonia to give a yellow precipitate which was filtered off, washed, and dried in a desiccator. The dry material was crystallised from dry ligroin yielding the *pyridoacridine* as yellow needles, m. p. 144°. Yield, 0·6 g. (Found: C, 64·45; H, 5·7; N, 13·1. $C_{23}H_{24}N_4Cl_2$ requires C, 64·6; H, 5·6; N, 13·1%).

2 : 8-*Dichloro*-5-(γ-*butylaminopropylamino*)-3 : 4 : 2′ : 3′-*pyridoacridine*. (*a*) 2 : 5 : 8-Trichloro-3 : 4 : 2′ : 3′-pyridoacridine (0·5 g.) was condensed with γ-butylaminopropylamine (0·25 g.) in dry molten phenol as described for 2 : 8-dichloro-5-(γ-diethylaminopropylamino)-3 : 4 : 2′ : 3′-pyridoacridine. The *pyridoacridine* crystallised from dry ligroin as yellow needles, m. p. 131°. Yield, 0·2 g. (Found: C, 64·55; H, 5·7; N, 13·05. $C_{23}H_{24}N_4Cl_2$ requires C, 64·6; H, 5·6; N, 13·1%).

(*b*) Thionyl chloride (2·4 g.) was dissolved in chloroform (10 c.c.) which had been dried over phosphoric oxide, and the solution added to a suspension of 4 : 8′-dichloro-6′-quinolylanthranilic acid (6 g.) in dry chloroform (80 c.c.). The mixture was maintained at room temperature for 3½ hours and then boiled under reflux for a further hour. The chloroform and excess of thionyl chloride were then removed by distillation and the bright yellow residue, presumably 4 : 8′-dichloro-6′-quinolylanthranilic acid chloride, was dissolved in dry chloroform (34 c.c.). A solution of γ-butylaminopropylamine (2·6 g.) in dry chloroform (10 c.c.) was added and the mixture heated under reflux for 1 hour. A small amount of white sublimate formed in the condenser melted at 325° but was not identified. The chloroform solution was filtered and the chloroform removed from the filtrate leaving a dark reddish-brown oil, probably 4 : 8′-dichloro-6′-quinolylanthranil-(γ-butylaminopropyl)amide hydrochloride. This was refluxed with phosphoryl chloride (20 c.c.) for 2 hours in an oil-bath at 150°; hydrogen chloride was evolved. The excess of phosphoryl chloride was removed under reduced pressure and the thick dark red oil remaining was dissolved in ice–water. The brown solution so obtained was filtered and the filtrate made alkaline

with ammonia; crude 2 : 8-dichloro-5-(γ-monobutylaminopropylamino)-3 : 4 : 2′ : 3′-pyridoacridine was thus obtained as a yellowish solid in poor yield and was crystallised from ligroin, m. p. 130°. A mixed melting point with a sample prepared by method (*a*) was not depressed.

6-*Nitro*-8-*methylquinoline*.—Concentrated sulphuric acid (440 c.c.) was added to water (343 c.c.) and to this diluted acid were added 5-nitro-*o*-toluidine (100 g.), glycerol (176 c.c.), and arsenic acid (194·5 c.c of 65% As_2O_5 solution). The mixture was brought slowly to the boil and refluxed gently for 8 hours at the end of which no unchanged amine could be detected by the diazo-test. After cooling it was diluted with its own volume of water and basified with 10N-sodium hydroxide. The precipitate of 6-nitro-8-methylquinoline was filtered off, dried at 70° (yield, 97 g.), and crystallised from alcohol and then from benzene as whitish needles, m. p. 130° (Found: C, 63·75; H, 4·25. Calc. for $C_{10}H_8O_2N_2$: C, 63·8; H, 4·3%).

6-*Amino*-8-*methylquinoline*.—6-Nitro-8-methylquinoline (30·4 g.) was dissolved in boiling methylated spirit (100 c.c.) containing concentrated hydrochloric acid (5 c.c.), and iron filings (34 g.) were added in four portions at five-minute intervals. The mixture was kept boiling vigorously for two hours, the acid neutralised with 10N-sodium hydroxide solution, and the mixture then filtered hot and the residue well washed with hot spirit. The alcohol was distilled off on the water-bath and the residue crystallised from benzene to yield 6-amino-8-methylquinoline as buff-coloured needles, m. p. 129°. Yield, 20 g. Alternatively, the final crystallisation may be made from alcohol.

For analysis 6-*acetamido*-8-*methylquinoline* was prepared by heating 6-amino-8-methylquinoline (1 g.) with acetic anhydride (10 c.c.) under an air condenser for 2 hours in the water-bath. The mixture was poured into cold water, and a blue fluorescence then appeared. Addition of ammonia gave a cream precipitate which was filtered off, washed, and dried at 70°. The compound recrystallised from hot water in glistening white plates, m. p. 174—174·5° (Found: C, 71·95; H, 5·75. $C_{12}H_{12}ON_2$ requires C, 72·0; H, 6·0%).

4-*Chloro*-(8′-*methyl*-6′-*quinolyl*)*anthranilic Acid*.—6-Amino-8-methylquinoline (31·8 g.), potassium 2 : 4-dichlorobenzoate (46·2 g.), copper bronze (0·1 g.), and amyl alcohol (60 c.c.) were heated under reflux in an oil-bath at 150° for 6 hours. The amyl alcohol was removed by filtration, and the residue well washed with acetone and extracted with a large volume of hot dilute ammonia. Alternatively, the amyl alcohol can be removed by distillation in steam and the residue filtered off and extracted with ammonia as before. Acidification of the ammoniacal extract with acetic acid yielded a small amount of the required acid (8%). A further yield was obtained from the residue insoluble in ammonia, which was found to be completely soluble in hot 2N-hydrochloric acid. On cooling, the hydrochloride of the acid separated, was filtered off and dissolved in hot 2N-hydrochloric acid, and ammonia added to precipitate the acid (72%) as a pale yellow compound which crystallised from alcohol as buff-coloured needles, m. p. 275°. Total yield, 48 g.

The *ethyl* ester was prepared by refluxing the acid (0·5 g.), ethyl alcohol (10 c.c.), and concentrated sulphuric acid (4 c.c.) for 1 hour. The mixture was allowed to cool, poured on ice, and, after ½ hour, made alkaline with ammonia. The grey precipitate so produced recrystallised from alcohol in light brown needles, m. p. 74° (Found: C, 66·8; H, 5·1; N, 8·1. $C_{19}H_{17}O_2N_2Cl$ requires C, 67·0; H, 5·0; N, 8·2%).

8-*Chloro*-2-*methyl*-3 : 4 : 2′ : 3′-*pyridoacridone*.—4-Chloro-(8′-methyl-6′-quinolyl)anthranilic acid (5 g.) and concentrated sulphuric acid (50 c.c.) were mixed in a round-bottomed flask, maintained at 100° for 4 hours, allowed to cool, and poured on ice. The yellow-brown precipitate, presumably the sulphate of the *pyridoacridone*, was filtered off, suspended in water, and excess of ammonia added. The flocculent precipitate was separated, washed, dried, and crystallised from alcohol as yellow needles, m. p. 383° (decomp.) (Found: C, 67·6; H, 3·9; N, 9·65. $C_{17}H_{11}ON_2Cl,\frac{1}{2}H_2O$ requires C, 67·2; H, 4·0; N, 9·2%).

5 : 8-*Dichloro*-2-*methyl*-3 : 4 : 2′ : 3′-*pyridoacridine*.—8-Chloro-2-methyl-3 : 4 : 2′ : 3′-pyridoacridone (10 g.), phosphorus pentachloride (4 g.), and phosphoryl chloride (60 c.c.) were refluxed for 6 hours in an oil-bath at 150°. The product was worked up as described for 2 : 5-dichloro-3 : 4 : 2′ : 3′-pyridoacridine. The crude product (10 g., m. p. 217—218°), crystallised from dry benzene, gave yellow needles of the *pyridoacridine*, m. p. 232°. Yield, 6 g. (Found: C, 65·75; H, 3·5; N, 8·7; Cl, 21·5. $C_{17}H_{10}N_2Cl_2$ requires C, 65·2; H, 3·2; N, 8·95; Cl, 22·7%).

8-*Chloro*-2-*methyl*-5-(γ-*diethylaminopropylamino*)-3 : 4 : 2′ : 3′-*pyridoacridine*.—This *compound* was prepared from 5 : 8-dichloro-2-methyl-3 : 4 : 2′ : 3′-pyridoacridine (1 g.) and γ-diethylaminopropylamine (0·5 g.) in dry phenol (10 g.) as described under the preparation of 2 : 8-dichloro-5-(γ-diethylaminopropylamino)-3 : 4 : 2′ : 3′-pyridoacridine. Yield, 0·4 g.; m. p. 110° (Found: C, 70·3; H, 6·45; N, 13·9. $C_{24}H_{27}N_4Cl$ requires C, 70·9; H, 6·6; N, 13·8%).

We are indebted to Imperial Chemical Industries Limited for facilities in connection with the above work, and express our thanks to them for a grant to one of us (W. C. H.), and to their analytical department for the microanalyses.

RESEARCH LABORATORY, ROYAL COLLEGE OF PHYSICIANS,
EDINBURGH.

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131. *Thiohydantoins. Part I. Preparation of 5 : 5-Disubstituted 2 : 4-Dithiohydantoins from the Corresponding Ketones.*

By H. C. CARRINGTON.

Ketones are converted into 5 : 5-disubstituted 2 : 4-dithiohydantoins by reaction with carbon disulphide and ammonium cyanide (or a mixture of salts capable of reacting as such) in aqueous methyl-alcoholic solution.

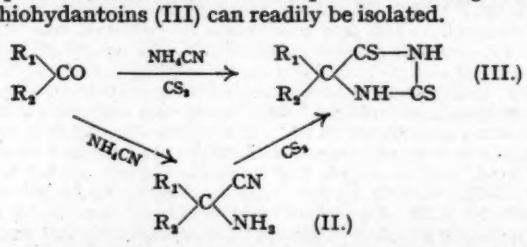
THE replacement of the oxygen atom in the 2-position of the 5 : 5-dialkylbarbituric acids by sulphur has a marked effect on their hypnotic action. For instance, the duration of action of 5-ethyl-5-α-methylbutylbarbituric acid is greatly diminished on passing to the corresponding 2-thio-derivative, and the increased control over the depth of hypnosis given by this rapid detoxication or elimination has made possible the widespread use of 5-ethyl-5-α-methylbutyl-2-thiobarbituric acid as an intravenous anæsthetic.

The 5 : 5-disubstituted hydantoins are much less powerful hypnotics than the corresponding barbituric acids, but nevertheless it appeared possible that the replacement of the oxygen atoms by sulphur in this series, too, might lead to hypnotics of value. This paper is the first of a short series in which the chemical work involved in the preparation of a large number of thiohydantoin derivatives will be described. The results of their pharmacological examination will be reported elsewhere.

The conversion of aldehydes and ketones into 5-substituted hydantoins by the action of sodium cyanide and ammonium carbonate (Bucherer and Steiner, *J. pr. Chem.*, 1934, **140**, 291) is well-known. During the development of this method, Bucherer and Lieb (*ibid.*, **141**, 5) made some attempts to extend the procedure to the preparation of 5-substituted 2 : 4-dithiohydantoins. They studied the reaction of the cyanohydrins from acetone and *cyclo*hexanone with ammonia and carbon disulphide under various conditions, and also the action of carbon disulphide on α-amino*iso*butyronitrile (II; $R_1 = R_2 = Me$). In no case did they identify the expected 2 : 4-dithiohydantoins among the products of the reactions.

Later, it was claimed by Jacobson (U.S.P., 2,143,816, 1939) that despite the failure of Bucherer and Lieb 2 : 4-dithiohydantoins could be obtained by the action of carbon disulphide on α-amino-nitriles, and his examples included the preparation of 5 : 5-dimethyl-2 : 4-dithiohydantoin (III; $R_1 = R_2 = Me$) from α-amino*iso*butyronitrile. Henze and Smith (*J. Amer. Chem. Soc.*, 1943, **65**, 1090) treated several 5 : 5-disubstituted hydantoins with phosphorus trisulphide in a hydrocarbon solvent to give the corresponding 2 : 4-dithio-derivatives.

In a reinvestigation of the application of the Bucherer reaction to the preparation of dithiohydantoins it has been found that when ketones (I) react with carbon disulphide and ammonium cyanide (or, in practice, a mixture of salts capable of reacting as ammonium cyanide) the corresponding 2 : 4-dithiohydantoins (III) can readily be isolated.



It is clearly possible that the α-amino-nitriles (II) are intermediates in this reaction. Of a wide variety of ketones employed, only di*iso*propyl ketone and camphor have failed to give the corresponding 2 : 4-dithiohydantoins. The reaction can be carried out in a variety of ways. For example, in the preparation of 5 : 5-cyclo*pentamethylene*-2 : 4-*dithiohydantoin* (III, $R_1R_2 = [CH_2]_5$) from *cyclo*hexanone, solvents such as aqueous methyl alcohol, ethyl alcohol, and benzene have been used. The best yields may be obtained by conducting the experiments under pressure at about 80°, but, in general, boiling under reflux in aqueous methyl alcohol is the most convenient procedure.

The failure of Bucherer and Lieb to obtain or identify the 2 : 4-dithiohydantoins in their experiments is difficult to understand. In studies of the action of ammonia and carbon disulphide on *cyclo*hexanone cyanohydrin they described a number of products, among which, in one experiment, was a yellow crystalline substance of m. p. 265°, which was not further investigated. This may well have been the dithiohydantoin which they were seeking. In experiments with acetone cyanohydrin, ammonia, and carbon disulphide, or α-amino*iso*butyronitrile and carbon disulphide they described one product of m. p. 155°, which has not been encountered in the present studies, and one of m. p. 297°, which was probably identical with that obtained as a by-product in the procedure now given. The structure of this compound will be discussed in the next paper.

EXPERIMENTAL.

Conversion of Ketones into Dithiohydantoins.—The early experiments were carried out under pressure the following being a typical procedure.

5 : 5-*Dimethyl*-2 : 4-*dithiohydantoin*. Acetone (58 g.), sodium cyanide (51 g.), ammonium chloride (55 g.), carbon disulphide (76 g.), and industrial ethyl alcohol (100 c.c.) were heated together in an autoclave at 80—85° for 8 hours. After collection of the solid residue, and washing it with ethyl alcohol, the united filtrate and washings were treated with carbon, and evaporated to a syrup, which crystallised on standing. It was purified by dissolving it in sodium hydroxide solution, treating the solution with carbon, filtering it, and reprecipitating the hydantoin with hydrochloric acid. It recrystallised from benzene in long, pale yellow needles, m. p. 144° (50 g., 31%) (Found: C, 37·8; H, 5·2; N, 17·45; S, 40·1. Calc. for $C_5H_8N_2S_2$: C, 37·5; H, 5·0; N, 17·45; S, 40·0%).

In a similar way, equivalent amounts of the corresponding ketones being used, there were obtained: 5 : 5-*diethyl*-2 : 4-*dithiohydantoin*, bright yellow needles, m. p. 155°, from aqueous methyl alcohol (yield, 37%) (Found: N, 15·0; S, 33·8. $C_7H_{12}N_2S_2$ requires N, 14·9; S, 34·0%); 5 : 5-*di*-n-*propyl*-2 : 4-*dithiohydantoin*, pale yellow needles, m. p. 111—112°, from light petroleum (b. p. 100—120°) (yield, 16%) (Found: N, 13·2; S, 29·2. $C_{10}H_{16}N_2S_2$ requires N, 13·0; S, 29·6%); 5-phenyl-5-methyl-2 : 4-dithiohydantoin, bright yellow needles, m. p. 173—174°, from aqueous methyl alcohol (yield, 2%; 55% of the acetophenone was recovered unchanged) (Found: N, 12·6; S, 29·1. Calc. for $C_{10}H_{10}N_2S_2$: N, 12·5; S, 28·9%).

In later experiments, a standard procedure was adopted of heating the ketone under reflux at 50—55° for 20—24 hours with equivalent amounts of ammonium chloride, sodium cyanide, and carbon disulphide, the whole being maintained in solution in aqueous alcohol. The solvents, any unchanged ketone, and carbon disulphide were removed by steam-distillation, and the product, which separated either as a solid or as an oil which solidified on cooling, was purified by recrystallisation, usually from aqueous methyl alcohol. With some of the cyclic ketones, the product crystallised directly from the reaction mixture either during the reaction or on cooling. The results of these experiments are summarised in the table.

2 : 4-Dithiohydantoin. 5 : 5-Substituents.	Formula.	M. p.	Yield, %.	Analysis. Found, N %.	Analysis. Required, N %.
5 : 5-Dimethyl	$C_5H_8N_2S_2$	144°	27	—	—
5-Methyl-5-ethyl	$C_6H_{10}N_2S_2$	147—148	15	16·1	16·1
5 : 5-Diethyl	$C_7H_{12}N_2S_2$	155	10	—	—
5-Methyl-5-*n*-propyl	$C_7H_{12}N_2S_2$	123—124	10	14·55	14·9
5-Methyl-5-*iso*propyl	$C_7H_{12}N_2S_2$	225—226	7·5	15·15	14·9
5-Methyl-5-*iso*butyl	$C_8H_{14}N_2S_2$	91—92	10	13·65	13·85
5-Methyl-5-*tert.*-butyl	$C_8H_{14}N_2S_2$	235—236	5	13·7	13·85
5-Methyl-5-*n*-amyl	$C_9H_{16}N_2S_2$	117—118	14	12·4	13·0
5-Methyl-5-*iso*hexenyl	$C_{10}H_{16}N_2S_2$	99	13	12·3	12·3
5-Methyl-5-*cyclo*hexyl	$C_{10}H_{16}N_2S_2$	190	7	12·1	12·3
5-Benzyl-5-methyl	$C_{11}H_{12}N_2S_2$	156	9	11·7	11·8
5-β-Phenylethyl-5-methyl	$C_{12}H_{14}N_2S_2$	180	22	10·9	11·2
5 : 5-*cyclo*Tetramethylene (*a*)	$C_9H_{16}N_2S_2$	242—243	27	15·2	15·0
5 : 5-2′-Methyl*cyclo*tetramethylene (*b*)	$C_9H_{12}N_2S_2$	232	25	13·5	14·0
5 : 5-*cyclo*Pentamethylene (*c*)	$C_9H_{12}N_2S_2$	267	36	13·7	14·0
5 : 5-1′-Methyl*cyclo*pentamethylene (*d*)	$C_9H_{14}N_2S_2$	184	10	12·8	13·1
5 : 5-2′-Methyl*cyclo*pentamethylene (*e*)	$C_9H_{14}N_2S_2$	203	32	12·65	13·1
5 : 5-3′-Methyl*cyclo*pentamethylene (*f*)	$C_9H_{14}N_2S_2$	255	38	13·0	13·1
5 : 5-*cyclo*Hexamethylene (*g*)	$C_9H_{14}N_2S_2$	242	21	13·1	13·1
5 : 5-1′ : 3′-Dimethyl*cyclo*pentamethylene (*h*)	$C_{10}H_{16}N_2S_2$	172	13	12·0	12·3
5 : 5-1′ : 4′-Dimethyl*cyclo*pentamethylene (*i*)	$C_{10}H_{16}N_2S_2$	197	14	12·35	12·3
5 : 5-2′ : 4′-Dimethyl*cyclo*pentamethylene (*j*)	$C_{10}H_{16}N_2S_2$	230	20	11·75	12·3
5 : 5-4′-Methyl*iso*propyl*cyclo*pentamethylene (*k*)	$C_{12}H_{20}N_2S_2$	209	5	10·5	10·9

(*a*) From *cyclo*pentanone. (*b*) From 3-methyl*cyclo*pentanone. (*c*) From *cyclo*hexanone. (*d*) From 2-methyl*cyclo*hexanone. (*e*) From 3-methyl*cyclo*hexanone. (*f*) From 4-methyl*cyclo*hexanone. (*g*) From *cyclo*heptanone. (*h*) From 2 : 4-dimethyl*cyclo*hexanone. (*i*) From 2 : 5-dimethyl*cyclo*hexanone. (*j*) From 3 : 5-dimethyl*cyclo*hexanone. (*k*) From menthone.

Attempts to prepare the dithiohydantoins from di*iso*propyl ketone and camphor by this method were unsuccessful, the ketone being recovered unchanged. Except 5 : 5-dimethyl- and 5-phenyl-5-methyl-2 : 4-dithiohydantoin, all the dithiohydantoins described above are new.

When 5 : 5-dimethyl-2 : 4-dithiohydantoin was prepared by this method, there was also obtained a by-product, very sparingly soluble in methanol, crystallising from water as small colourless prisms, m. p. 300° (decomp.).

Part of the work described in this paper formed the subject matter of B.P. 512,629. The author wishes to thank Mr. E. S. Morton, who carried out the microanalyses.

RESEARCH LABORATORIES, IMPERIAL CHEMICAL INDUSTRIES, LTD.,
BLACKLEY, MANCHESTER 9.

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132. *Thiohydantoins. Part II. Conversion of 5 : 5-Disubstituted 2 : 4-Dithiohydantoins into the Corresponding Monothiohydantoins.*

By H. C. Carrington.

5 : 5-Disubstituted 2 : 4-dithiohydantoins react with ammonia or primary amino-compounds to give 5 : 5-disubstituted 4-imino(or substituted imino)-2-thiohydantoins, which are readily hydrolysed by acid to the corresponding 2-thiohydantoins. In one case studied, methylation of a 5 : 5-disubstituted 2 : 4-dithiohydantoin in alkaline solution with methyl sulphate led to the formation of the corresponding 4-thiohydantoin, methylthiol being liberated.

Two series of monothiohydantoin derivatives are possible, with CS replacing the CO groups in either the 2- or the 4-position, and members of both series are known. A well-established route to the 2-thiohydantoins is that of Johnson and Scott (*J. Amer. Chem. Soc.*, 1913, **35**, 1130) wherein α-amino-acids or their acyl derivatives are caused to react with ammonium thiocyanate and acetic anhydride to give the acyl derivatives of 2-thiohydantoins, which are then deacylated by acid hydrolysis. The 4-thiohydantoins are less well known, but the parent substance was prepared by Johnson and Chernoff (*J. Amer. Chem. Soc.*, 1912, **34**, 1208) by addition of hydrogen sulphide to carbethoxyaminoacetonitrile and conversion of the resulting carbethoxyaminothionacetamide into 4-thiohydantoin by the action of alkali.

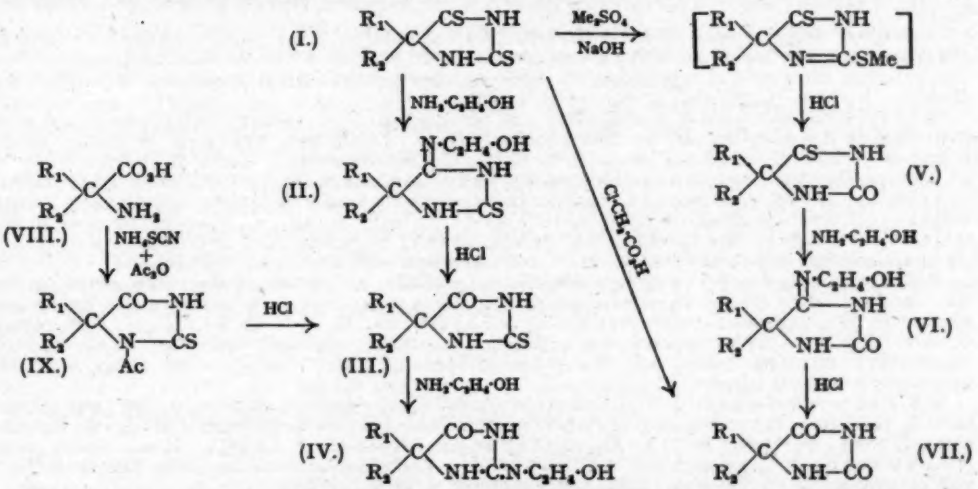
It seemed possible that easier routes to the 5 : 5-disubstituted monothiohydantoins might be achieved by partial hydrolysis of the now readily available 2 : 4-dithiohydantoins (see preceding paper). Johnson, Pfau, and Hodge (*J. Amer. Chem. Soc.*, 1912, **34**, 1041) showed that many 2-thiohydantoins could be desulphurised by heating with aqueous chloroacetic acid, and 4-thiohydantoin is converted into hydantoin by the action of hydrochloric acid (Johnson and Chernoff, *loc. cit.*). In preliminary experiments it was found that 5 : 5-dimethyl-2 : 4-dithiohydantoin (I, $R_1 = R_2 = Me$) was converted into the corresponding 2-thio-compound (III, $R_1 = R_2 = Me$) by heating with 20% hydrochloric acid, but higher members of the series, such as the 5 : 5-diethyl and the 5 : 5-*cyclo*pentamethylene derivative were unchanged by this treatment. Boiling 20% aqueous chloroacetic acid completely removed the sulphur from 5 : 5-*cyclo*pentamethylene-2 : 4-dithiohydantoin (I, $R_1R_2 = [CH_2]_5$), but intermediate compounds were not readily isolated. It therefore appeared that some other general method was desirable.

When 5 : 5-dimethyl-2 : 4-dithiohydantoin was treated with warm aqueous ammonia, hydrogen sulphide was evolved, and a sparingly soluble white crystalline product separated, which was identical with the by-product obtained in the preparation of the dithiohydantoin by the method described in Part I. This substance has now been shown to be *4-imino-5 : 5-dimethyl-2-thiohydantoin*. Its empirical formula, $C_5H_9N_3S$, showed that $>S$ in the dithiohydantoin had been replaced by $>NH$, and on hydrolysis with hot hydrochloric acid it gave 5 : 5-dimethyl-2-thiohydantoin, m. p. 179°, identical with the product obtained by the action of hydrochloric acid on the dithiohydantoin, and also with that synthesised from α-amino*iso*butyric acid (VIII, $R_1 = R_2 = Me$) by the method of Johnson and Scott (*loc. cit.*). Komatsu (*Mem. Coll. Sci. Kyoto Imp. Univ.*, 1914, **1**, 69; *A.*, 1915, **108**, i, 168) had already described a synthesis of 5 : 5-dimethyl-2-thiohydantoin by a method similar to that of Johnson and Scott, but his product had m. p. 163—164°, and the identity of the compound now under investigation was uncertain until a repetition of Komatsu's synthesis led to the isolation by an unequivocal route of 5 : 5-dimethyl-2-thiohydantoin in a pure condition, m. p. 179°.

The preferential attack of ammonia on the 4-thio-group of the dithiohydantoin corresponds with results previously described in the closely similar 5 : 5-diethyl-2 : 4-dithio- and -2 : 4 : 6-trithio-barbituric acids (Carrington, *J.*, 1944, 124). There, too, it was shown that the sulphur atoms of " thioamide " type in the 4- and 6-positions were replaced by ammonia in preference to the 2-thio-atoms of " thiourea " type.

Other primary amino-compounds reacted with 5 : 5-dimethyl-2 : 4-dithiohydantoin in a similar way. Thus, with hydrazine hydrate, *4-hydrazino-5 : 5-dimethyl-2-thiohydantoin* was produced, and aqueous 2-aminoethyl alcohol gave *4-2′-hydroxyethylimino-5 : 5-dimethyl-2-thiohydantoin* (II, $R_1 = R_2 = Me$), both of which were readily hydrolysed by hot hydrochloric acid to 5 : 5-dimethyl-2-thiohydantoin. The reaction with 2-aminoethyl alcohol, and subsequent hydrolysis of the 2-hydroxyethyl-imino compounds has been used as a general method for the conversion of the 5 : 5-disubstituted 2 : 4-dithiohydantoins into the corresponding 2-thio-compounds. 2-Aminoethyl alcohol is a convenient amine on account of its low volatility. 5 : 5-*cyclo*Pentamethylene-2 : 4-dithiohydantoin gave *4-2′-hydroxyethylimino-5 : 5-*

cyclo*pentamethylene-2-thiohydantoin* (II, $R_1R_2 = [CH_2]_5$), hydrolysing to 5 : 5-cyclo*pentamethylene-2-thiohydantoin* (III, $R_1R_2 = [CH_2]_5$), which was also synthesised from 1-aminohexahydrobenzoic acid (VIII, $R_1R_2 = [CH_2]_5$) by the method of Johnson and Scott (*loc. cit.*). This monothiohydantoin again reacted with 2-aminoethyl alcohol to give 2-2′-*hydroxyethylimino*-5 : 5-cyclo*pentamethylenehydantoin* (IV, $R_1R_2 = [CH_2]_5$), which was much more stable to hydrolysis, being recovered unchanged after boiling with 20% hydrochloric acid. 5 : 5-(3′-Methyl*cyclo*pentamethylene)-2 : 4-dithiohydantoin with 2-aminoethyl alcohol similarly gave 4-2′-*hydroxyethylimino*-5 : 5-(3′-*methyl*cyclo*pentamethylene*)-2-*thiohydantoin*, which was readily hydrolysed to 5 : 5-(3′-*methyl*cyclo*pentamethylene*)-2-*thiohydantoin*.



When 5 : 5-*cyclo*pentamethylene-2 : 4-dithiohydantoin, dissolved in aqueous sodium hydroxide, reacted with methyl sulphate, and the product was acidified, methylthiol was evolved, and a second monothio-compound obtained. It differed from the 2-thio-compound in several respects. It was much higher melting, 240° compared with 191°, and was bright yellow, whereas the 2-thio-compound was colourless. It was shown to be 5 : 5-cyclo*pentamethylene-4-thiohydantoin* (V, $R_1R_2 = [CH_2]_5$) by reaction with 2-aminoethyl alcohol, whereby it gave 4-2′-*hydroxyethylimino*-5 : 5-cyclo*pentamethylenehydantoin* (VI, $R_1R_2 = [CH_2]_5$), which, in contrast to the isomeric 2-2′-hydroxyethylimino-compound described above, was readily hydrolysed by dilute hydrochloric acid to 5 : 5-*cyclo*pentamethylenehydantoin, identical with that obtained from *cyclo*hexanone by Bucherer and Steiner's method (*J. pr. Chem.*, 1934, **140**, 291).

The reaction of the dithiohydantoin with methyl sulphate would appear to proceed through an unstable intermediate 2-methylthio-derivative. This is in contrast with the results of an experiment in the barbituric acid series, where 5 : 5-diethyl-2 : 4 : 6-trithiobarbituric acid was found to be methylated in one of the " thioamide " positions, giving 6-methylthio-5 : 5-diethyl-2 : 4-dithiobarbituric acid (Carrington, *loc. cit.*).

Experimental.

1-*Acetyl*-5 : 5-*dimethyl*-2-*thiohydantoin*.—α-Amino*iso*butyric acid (20 g.), ammonium thiocyanate (25 g.), and acetic anhydride (70 c.c.) were warmed gently until reaction commenced, and when the initial vigorous reaction had subsided the mixture was boiled under reflux for ½ hour. It was cooled, poured into ice-water, and the solid product filtered off and crystallised from aqueous methyl alcohol; m. p. 186—187° (7 g.) (Found : N, 14·85; S, 17·6. Calc. for $C_7H_{10}O_2N_2S$: N, 15·05; S, 17·2%).

5 : 5-*Dimethyl*-2-*thiohydantoin*.—The acetyl derivative (1 g.) was heated under reflux for 1 hour with 20% hydrochloric acid (2 c.c.) and methyl alcohol (4 c.c.). The methyl alcohol was evaporated, and on cooling, 5 : 5-dimethyl-2-thiohydantoin crystallised in theoretical yield. Recrystallised from water, it had m. p. 178—179° (Found : C, 41·8; H, 5·6; N, 19·4; S, 22·3. Calc. for $C_5H_8ON_2S$: C, 41·7; H, 5·55; N, 19·45; S, 22·2%). The same product was obtained when 5 : 5-dimethyl-2 : 4-dithiohydantoin (2 g.) was heated under reflux for 4 hours with 20% hydrochloric acid (30 c.c.).

4-*Imino*-5 : 5-*dimethyl*-2-*thiohydantoin*.—5 : 5-Dimethyl-2 : 4-dithiohydantoin (2 g.) was warmed gently with aqueous ammonia (*d* 0·88, 6 c.c.). Hydrogen sulphide was evolved, and a white crystalline solid separated. After cooling, the *product* was filtered off and recrystallised from water; m. p. 300—302° (decomp.) (1·3 g.) (Found : C, 42·2; H, 6·1; N, 29·2; S, 22·4. $C_5H_9N_3S$ requires C, 41·85; H, 6·3; N, 29·4; S, 22·4%). It was identical with the by-product obtained in the preparation of 5 : 5-dimethyl-2 : 4-dithiohydantoin (see Part I), and on being heated under reflux for 1 hour with 20%

hydrochloric acid it was hydrolysed quantitatively to 5 : 5-dimethyl-2-thiohydantoin, m. p. 178—179°, identical with that described above.

4-*Hydrazino*-5 : 5-*dimethyl*-2-*thiohydantoin*.—5 : 5-Dimethyl-2 : 4-dithiohydantoin (2 g.) was dissolved in 50% hydrazine hydrate (5 c.c.). On warming, hydrogen sulphide was evolved and a white solid separated. After being cooled and collected, the *product* was recrystallised from ethyl alcohol; m. p. 188° (decomp.) (1·0 g.) (Found: N, 35·0; S, 19·8. $C_5H_{10}N_4S$ requires N, 35·4; S, 20·2%).

4-2′-*Hydroxyethylimino*-5 : 5-*dimethyl*-2-*thiohydantoin*.—5 : 5-Dimethyl-2 : 4-dithiohydantoin (5 g.) was heated to 100° for ½ hour with 50% aqueous 2-aminoethyl alcohol (20 c.c.). Hydrogen sulphide was evolved, and on cooling, the product crystallised. After recrystallising from ethyl alcohol, it had m. p. 223—224° (3 g.) (Found: N, 22·5; S, 17·55. $C_7H_{13}ON_3S$ requires N, 22·5; S, 17·1%).

Both the 4-hydrazino- and the 4-2′-*hydroxyethylimino*-compound were hydrolysed quantitatively to 5 : 5-dimethyl-2-thiohydantoin when heated under reflux for 1 hour with ten parts of 20% hydrochloric acid.

1-*Acetyl*-5 : 5-cyclo*pentamethylene*-2-*thiohydantoin* was obtained from 1-aminohexahydrobenzoic acid (35 g.), ammonium thiocyanate (50 g.), and acetic anhydride (140 c.c.) by the method described above. The product, after several crystallisations from aqueous methyl alcohol, had m. p. 165—167° (5 g.) (Found: N, 12·4. $C_{10}H_{14}O_2N_2S$ requires N, 12·4%).

5 : 5-cyclo*Pentamethylene*-2-*thiohydantoin* was obtained in 85% yield by hydrolysis of the acetyl derivative in a similar manner to that described above. Crystallised from aqueous methyl alcohol, it had m. p. 192° (Found: N, 15·05; S, 17·3. $C_8H_{12}ON_2S$ requires, N, 15·2; S, 17·4%).

4-2′-*Hydroxyethylimino*-5 : 5-cyclo*pentamethylene*-2-*thiohydantoin*, m. p. 245° (from ethyl alcohol), was obtained in 62% yield from 5 : 5-*cyclo*pentamethylene-2 : 4-dithiohydantoin and aqueous 2-aminoethyl alcohol, by the method described above (Found: N, 18·2; S, 14·4. $C_{10}H_{17}ON_3S$ requires N, 18·5; S, 14·1%). It was readily hydrolysed in theoretical yield by boiling 20% hydrochloric acid to 5 : 5-*cyclo*pentamethylene-2-thiohydantoin, m. p. 192°, identical with that described above.

2-2′-*Hydroxyethylimino*-5 : 5-cyclo*pentamethylenehydantoin*, m. p. 243° (0·8 g. from ethyl alcohol), was obtained when 5 : 5-*cyclo*pentamethylene-2-thiohydantoin (2 g.) was heated under reflux for 2 hours with 50% aqueous 2-aminoethyl alcohol (8 c.c.) (Found: C, 56·7; H, 8·1. $C_{10}H_{17}O_2N_3$ requires C, 56·9; H, 8·1%). This compound was much more resistant to acid hydrolysis than the 4-2′-hydroxyethylimino-isomer (see below) and was recovered unchanged after boiling under reflux with 20% hydrochloric acid for 5 hours.

4-2′-*Hydroxyethylimino*-5 : 5-(3′-*methyl*cyclo*pentamethylene*)-2-*thiohydantoin*, m. p. 234°, was obtained in 65% yield from the corresponding dithiohydantoin and aqueous 2-aminoethyl alcohol as described above (Found: N, 17·35; S, 13·3. $C_{11}H_{19}ON_3S$ requires N, 17·45; S, 13·3%). It was readily hydrolysed by boiling 20% hydrochloric acid to 5 : 5-(3′-*methyl*cyclo*pentamethylene*)-2-*thiohydantoin*, m. p. 219° (Found: N, 14·0; S, 16·4. $C_9H_{14}ON_2S$ requires N, 14·15; S, 16·2%).

5 : 5-cyclo*Pentamethylene*-4-*thiohydantoin*.—5 : 5-*cyclo*Pentamethylene-2 : 4-dithiohydantoin (8 g.) in 8% sodium hydroxide solution (60 c.c.) was treated at 10° with methyl sulphate (6 g.), added during 15 minutes with stirring. The mixture was stirred for 3 hours and a small quantity of low-melting solid was separated. (This had m. p. 42—45°, was not readily purified, and was not investigated further.) The aqueous solution was acidified, whereupon methylthiol was evolved, and a pale yellow solid separated. It was filtered off, and purified first through the sparingly soluble sodium salt, and then by crystallisation from aqueous methyl alcohol, to give the 4-*thio-compound* as shining yellow plates, m. p. 240° (2·0 g.) (Found: C, 52·4; H, 6·7; N, 14·85; S, 17·7. $C_8H_{12}ON_2S$ requires C, 52·2; H, 6·5; N, 15·2; S, 17·4%).

4-2′-*Hydroxyethylimino*-5 : 5-cyclo*pentamethylenehydantoin*, m. p. 255° (decomp.) (from methyl alcohol), was obtained in 40% yield by the action of aqueous 2-aminoethyl alcohol on the 4-thiohydantoin (Found: C, 56·6; H, 8·0; N, 19·75. $C_{10}H_{17}O_2N_3$ requires C, 56·9; H, 8·1; N, 19·9%). A mixed m. p. with the 2-2′-hydroxyethylimino-isomer (m. p. 243°, above) was 220—225°. The 4-2′-hydroxyethylimino-compound was readily hydrolysed by heating at 100° for ½ hour with 10% hydrochloric acid, to give 5 : 5-*cyclo*pentamethylenehydantoin, m. p. 217°, identical with material prepared from *cyclo*hexanone by Bucherer and Steiner's method (*loc. cit.*).

5 : 5-*cyclo*Pentamethylenehydantoin was also produced in almost quantitative yield when the corresponding dithio-derivative was heated under reflux with 20% aqueous chloroacetic acid for 5 hours.

The author wishes to thank Mr. E. S. Morton, who carried out the microanalyses.

RESEARCH LABORATORIES, IMPERIAL CHEMICAL INDUSTRIES, LTD.,
BLACKLEY, MANCHESTER, 9.

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133. *On the Suitability of Parasantonide for Asymmetric Photolysis.*

By STOTHERD MITCHELL and ERIC J. Y. SCOTT.

Parasantonide has been photolysed (in alcoholic solution) with mercury lines lying within each of its two ultra-violet absorption bands, and quantum efficiencies of 0·85 (for λ = 3132—2895 A.) and 0·40 (for λ = 2650—2537 A.) have been obtained. From these results and from absorption and rotatory-dispersion measurements made with irradiated solutions, it is concluded that racemic parasantonide would fulfil the conditions necessary for asymmetric photochemical work with wave-lengths in the neighbourhood of 3000 A.

THE keto-lactones known as santonide and parasantonide have similar absorption curves with well-defined maxima in the ultra-violet at about 3000 A. and 2350 A., respectively. Mitchell

and Schwarzwald (*J.*, 1939, 889) investigated the Cotton phenomena associated in each case with the first maximum and found normal anisotropy factors but exceptionally large specific rotations, those of parasantonide being the largest hitherto recorded. In the course of these experiments, a decrease in rotation was observed when solutions of both substances were exposed to ultra-violet light, so it was thought that they might be useful for the study of asymmetric photolysis if available in the racemic form. The *r*-santonin required for preparing them in this form appeared to be inaccessible at the time, but the recent work of Paranjape, Phalnikar, Bhide, and Nargund (*Rasayanam*, 1943, 1, 233) has indicated the possibility of obtaining it by synthesis. Before embarking on synthetic work, however, we have carried out some further experiments with *d*-parasantonide in order to determine to what extent it satisfies the photochemical conditions necessary for asymmetric photolysis, which may be summarised as (1) a quantum efficiency ≈ 1 with the absence of chain and dark reactions, and (2) destruction (by the light) of the asymmetric centre producing the Cotton effect.

Preliminary Experiments.—Alcoholic solutions of parasantonide were first exposed in fused-silica tubes to the full radiation from a mercury-vapour lamp. During irradiation there was no evolution of gas, nor was there any absorption of atmospheric oxygen. The change in rotation (α_D) with time of irradiation was then studied, and the results are given in Table I, where c denotes the original concentration of parasantonide in g./100 ml. of alcoholic solution, and the other symbols have their usual significance. When wave-lengths below 2800 A. (*i.e.*, beyond the first band) were cut off by placing a sheet of mica in front of the reaction tube the final rotation remained positive, but when wave-lengths within the first band were removed with a chlorine filter the residual rotation became negative.

TABLE I.

α_D for solutions during irradiation.

With mica inserted: $c = 3{\cdot}040$ g./100 ml.; $l = 0{\cdot}75$ dm.; $t = 17°$.

α_D	+18·79°	+10·72°	+6·78°	+3·18°	+2·04°	+1·68°
Time (hours)	0	10·5	18·5	33·5	48	62·5
α_D	+ 1·54°	+ 1·48°	+1·44°	+1·30°	+1·28°	+1·28°
Time	77	92	106·5	135·5	150	165

With chlorine filter inserted: $c = 1{\cdot}740$ g./100 ml.; $l = 0{\cdot}75$ dm.; $t = 17°$.

α_D	+10·96°	+8·58°	+6·73°	+3·70°	+1·68°	+0·30°
Time (hours)	0	8	16	32	46	57
α_D	−0·52°	−1·92°	−2·60°	−3·02°	−3·18°	−3·18°
Time	65	89	109	133	149	165

Periods of irradiation up to about 16 hours were employed in these experiments. The solutions were then left in the dark overnight and sometimes for longer periods. Absence of dark reactions was established by frequently repeating readings before restarting the irradiation.

Quantum Efficiencies.—Measurements of γ were made with groups of mercury lines within each of the two absorption bands of parasantonide. With layers of solution 1 cm. thick and of the same concentrations as given in Table I, complete absorption was achieved by using a nickel–cobalt filter together with mica for $\lambda = 3132$—2895 A. and the chlorine filter for $\lambda = 2650$—2537 A. The amounts of photochemical decomposition were determined polarimetrically, and energy measurements were made with a large-surface Moll thermopile and galvanometer calibrated against a Hefner candle in the usual way (cf. Gerlach, *Physikal. Z.*, 1913, 14, 577). The results are set out in Table II, where λ is the approximate optical centre of the wave-band used for irradiation, c is the initial concentration of parasantonide in g./100 ml. of alcoholic solution, α is the initial rotation, α_n the rotation after exposure for time t_n, and α_∞ the final rotation after prolonged exposure, all rotations being measured at room temperature (17°) with sodium light (5893 A.) and $l = 0{\cdot}75$ dm.

Let α_p be the rotation due to unchanged parasantonide after time t_n; then

$$\alpha_p = \alpha(\alpha_n - \alpha_\infty)/(\alpha - \alpha_\infty)$$

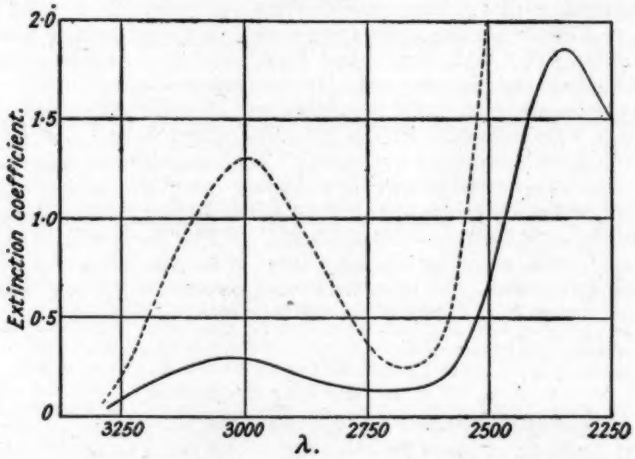
Hence, concentration of parasantonide after time $t_n = 100\alpha_p/l[\alpha] = c_n$ (in g./100 ml. solution); and number of g.-mols. decomposed $= (c - c_n) \times v/100M$, where v = volume of cell (7·24 ml.) and M is the molecular weight of parasantonide (246). The quantum efficiency γ is given by $\gamma = [$(g.-mols. decomposed)/(cals. absorbed)$] \times [(2{\cdot}847 \times 10^8)/\lambda]$. The second value for γ (0·40) although smaller than the first (0·85) is still appreciable and, in order to avoid loss of parasantonide, it will be advisable to cut off the shorter wave-lengths when experiments with

TABLE II.

λ, A.	t_n, mins.	c.	a.	a_n.	a_∞.	c_n.	G.-mols. decomposed.	Cals. absorbed.	γ.
3000	660	3·040	18·79°	17·08°	1·28°	2·744	$8·651 \times 10^{-5}$	9·69	0·85
2550	1110	1·740	10·96	10·02	−3·18	1·624	$3·396 \times 10^{-5}$	9·42	0·40

circularly polarised light are carried out. This precaution will also prevent any circular dichroism which may be associated with the second band from being effective.

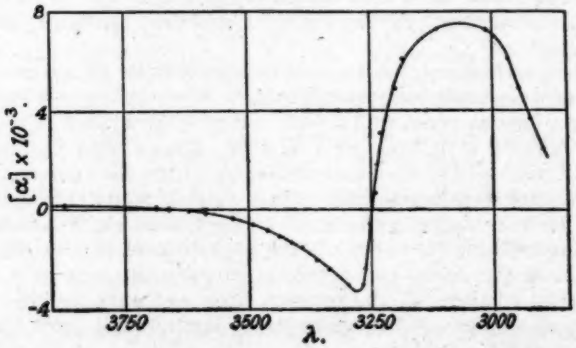
FIG. 1.



Absorption and Rotatory Dispersion Measurements.—Absorption and rotatory-dispersion curves were next constructed in order to study the effect of irradiation (by wave-lengths in the neighbourhood of 3000 A.) on the absorbing centre with which the Cotton effect in parasantonide is associated. Since we were unsuccessful in our attempts to isolate the products of photolysis in a crystalline state, we used irradiated solutions for this work.

Fig. 1 shows absorption curves drawn from readings taken with a Spekker ultra-violet spectrophotometer using 1-cm. cells. The broken curve was obtained with a non-irradiated

FIG. 2.



solution of parasantonide containing 0·03 g./100 ml. The solution after prolonged irradiation through mica (Table I) was diluted to correspond with this concentration and gave the continuous curve. It will be seen that the first band (max. 3000 A.), although much weakened, has not been completely destroyed by irradiation. The second band with its head at 2350 A. (not shown in the broken curve) is also present in a modified form.

Rotatory-dispersion measurements were made at room temperature (17°) with alcoholic solutions which had been irradiated through mica until α_D had become constant. Visual readings were taken with a Hilger polarimeter illuminated with light from a 100-c.p. Pointolite lamp after it had passed through a Zeiss–Winkel monochromator. For the photographic

readings we used the ultra-violet polarimeter described by Mitchell and Gordon (*J.*, 1936, 855) but substituted a Bellingham and Stanley polariser (half-shadow angle 6°) for the one previously employed. Table III contains the results. Specific rotations have been calculated (assuming the concentration c to be that of parasantonide before irradiation) to facilitate comparison with the values for non-irradiated parasantonide obtained by Mitchell and Schwarzwald (*loc. cit.*). In Fig. 2 [α] is plotted against λ.

TABLE III.

Rotatory-dispersion data for solutions after prolonged irradiation through mica.

Solutions: (*a*) $c = 1{\cdot}650$; (*b*) $c = 0{\cdot}165$; (*c*) $c = 0{\cdot}0825$ g./100 ml.

λ.	α.	[α].	λ.	α.	[α].
Solution (*a*): $l = 0{\cdot}75$ dm.					
Visual readings:					
7000	+0·41°	+ 33·1°	5500	+0·77°	+ 62·2°
6500	+0·52	+ 42·0	5000	+0·94	+ 76·0
5900	+0·64	+ 51·7	4750	+1·10	+ 88·9
Photographic readings:					
3870	+0·80	+ 64·6	3620	−1·00	− 80·8
3685	+0·40	+ 32·3	3585	−2·00	− 161·6
3660	0·00	0·0	3530	−4·00	− 323·2
Solution (*a*): $l = 0{\cdot}1$ dm.					
3490	−1·00	− 606·0	3410	−2·20	−1333
3460	−1·40	− 848·3	3390	−2·60	−1576
3435	−1·80	−1091	3360	−3·40	−2061
Solution (*b*): $l = 0{\cdot}1$ dm.					
3320	−0·40	−2425	3250	−0·10	− 606·0
3295	−0·50	−3031	3240	+0·10	+ 606·0
3265	−0·50	−3031	3235	+0·30	+1819
3260	−0·40	−2425	3230	+0·50	+3031
Solution (*c*): $l = 0{\cdot}1$ dm.					
3195	+0·40	+4849	2965	+0·50	+6060
3170	+0·50	+6060	2945	+0·40	+4849
3110	+0·60	+7273	2925	+0·30	+3637
3010	+0·60	+7273	2900	+0·20	+2425

Significance of the Results.—The results obtained by irradiation with wave-lengths within the first band (max. 3000 A.) allow us to conclude that racemic parasantonide would be suitable for asymmetric photochemical work. Absence of any chain reaction is shown by $\gamma = 0{\cdot}85$, and this value is sufficiently close to unity to make asymmetric photolysis a practical proposition, particularly as there is no dark reaction. Some loss of light would be caused, however, by the residual absorption (Fig. 1) which would act as an internal filter. The fall in rotation (α_D) from 18·79° to 1·28° (Table I) suggests that the Cotton effect associated with the first band in parasantonide has been destroyed by the irradiation. This is confirmed by the rotatory dispersion curve (Fig. 2). A "reversed" Cotton effect is now present in which the curve crosses the axis of zero rotation at 3250 A., not at 3000 A. as in parasantonide. Some negative ellipticity has also been detected in the neighbourhood of 3250 A.

EXPERIMENTAL.

Preparation of Parasantonide.—Santonin was first converted into santonic acid as described by Abkin and Medvedev (*J. Gen. Chem. Russia*, 1934, **4**, 1407; *A.*, 1935, 755). Cannizzaro and Valente's method (*Gazzetta*, 1878, **8**, 315) of preparing parasantonide from santonic acid was slightly modified. Santonic acid (10 g.) was refluxed with glacial acetic acid (50 ml.) for 5 hours. The solution was then treated in 5 portions, the first of which was transferred to a small distilling flask with the side arm fitting directly into a receiver, and the acetic acid was removed under reduced pressure. The apparatus was then filled with nitrogen and the flask heated slowly to between 260° and 300° on a metal-bath, with nitrogen bubbling through the viscous mass, which partly distilled. On reducing the pressure, a further amount of material passed into the receiver. The entire distillate was dissolved in ether, washed with dilute sodium carbonate solution, and dried (Na_2SO_4). This procedure was repeated for the other four portions, and the combined amounts of impure parasantonide obtained on distilling off the ether were crystallised from ether–light petroleum, and finally from light petroleum alone; m. p. 110°

Apparatus.—For all the irradiation experiments we used a Hewittic vacuum mercury-vapour lamp running at 4·5 amps. In determining γ with wave-lengths within the first band the infra-red, visible, and ultra-violet radiation down to 3200 A. were absorbed by a filter (215 g. of $NiSO_4.7H_2O$ and 60 g.

of $CoSO_4.7H_2O$ in 600 ml. of aqueous solution) contained in a 500-ml. fused-silica flask. The filter also acted as a condensing lens and suitable stops were arranged to eliminate stray light. A sheet of mica (0·05 mm. thick) for cutting off the ultra-violet below 2800 A. was placed just behind the final stop (5·5 × 0·5 cm.), and in front of it the reaction cell was fixed. This cell consisted of a fused-silica tube of square section (7·5 × 1 × 1 cm.) with a side tube for filling. A small piece of glass tubing about 1 cm. long was inserted for stirring, and glass ends of good optical quality were cemented in position. For measurements within the second band (λ = 2650—2537 A.) the apparatus was similar to that described above, but a chlorine filter was substituted for the mica plate. The chlorine was contained (at atmospheric pressure) in a fused silica cell, 8 cm. in diameter and 3 cm. thick (cf. Bowen, *J.*, 1935, 76).

We desire to thank the Carnegie Trust for a scholarship which enabled one of us (E. J. Y. S.) to take part in this work, and the Chemical Society for a grant with which a quantity of santonin was purchased.

UNIVERSITY OF GLASGOW [*Received, August 30th*, 1946.]

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134. *Attempts to find New Chemotherapeutic Amidines. Part VII.*

By J. O. HARRIS.

The preparation of 4 : 4′-*diamidino-2-methylstilbene* and 4 : 4′-*diamidino*-2 : 2′-*dimethylstilbene* as potential trypanocidal compounds is described.

THE high activity of 4 : 4′-diamidino-αβ-dimethylstilbene against *T. cruzi* (Barber, Slack, and Woolman, *J.*, 1943, 99) as compared with 4 : 4′-diamidinostilbene, together with the observation that certain nuclear substituents in the latter molecule enhanced its trypanocidal effect (Ashley and Harris, *J.*, 1946, 567), made the synthesis of 4 : 4′-*diamidino-2-methylstilbene* and 4 : 4′-*diamidino*-2 : 2′-*dimethylstilbene* desirable. The preparation of these compounds required the hitherto undescribed 5-*bromo*-o-*tolualdehyde* and 5-*bromo*-o-*tolylacetic* acid. Both these have been prepared from 5-bromo-*o*-toluic acid, the latter by the Arndt–Eistert reaction (*Ber.*, 1935, **68**, 200) and the former by the method of McFadyen and Stevens (*J.*, 1936, 584).

5-Bromo-*o*-tolylacetic acid was condensed with 4-cyanobenzaldehyde under the conditions of the Perkin reaction. The resulting cis-4-*bromo*-4′-*cyano*-2-*methylstilbene*-α-*carboxylic acid* was decarboxylated to yield cis-4-*bromo*-4′-*cyano*-2-*methylstilbene*, which with cuprous cyanide in pyridine gave cis-4 : 4′-*dicyano*-2-*methylstilbene*. It was observed that whilst the latter compound readily isomerised to the *trans*-isomer with iodine in nitrobenzene, the former under similar conditions remained unchanged. Conversion of either the *cis*- or the *trans*-dicyanide into the amidine by the method of Pinner ("Die Imido Äther") gave trans-4 : 4′-*diamidino*-2-*methylstilbene*.

An attempt to obtain *cis*-4-bromo-4′-cyano-2-methylstilbene by the method of Meerwein (*J. pr. Chem.*, 1939, **152**, 237) from *p*-cyanocinnamic acid and diazotised 5-bromo-*o*-toluidine gave a product from which the required substance could be isolated only with considerable difficulty and in too small a yield for preparative purposes.

The Perkin condensation between 5-bromo-*o*-tolylacetic acid and 5-bromo-*o*-tolualdehyde yielded in addition to cis-4 : 4′-*dibromo*-2 : 2′-*dimethylstilbene*-α-*carboxylic acid* small amounts of trans-4 : 4′-*dibromo*-2 : 2′-*dimethylstilbene* and 4-*bromo*-2-*methylcinnamic acid*.

cis-4 : 4′-*Dibromo*-2 : 2′-*dimethylstilbene*-α-*carboxylic acid* did not undergo decarboxylation on being heated in a vacuum or with copper chromite in quinoline. However, as anticipated, replacement of bromine with the more electron seeking $-CN$ group facilitated decarboxylation, since treatment of the above acid with cuprous cyanide in pyridine followed by high vacuum sublimation yielded cis-4 : 4′-*dicyano*-2 : 2′-*dimethylstilbene*. This was converted into trans-4 : 4′-*diamidino*-2 : 2′-*dimethylstilbene* which was prepared in better yield from trans-4 : 4′-*dicyano*-2 : 2′-*dimethylstilbene* obtained by inversion of the *cis*-isomer.

These amidines have been tested for trypanocidal activity; the results will be discussed elsewhere.

EXPERIMENTAL.

5-*Bromo*-o-*toluoyl Chloride*.—5-Bromo-*o*-toluic acid (34 g.) was refluxed on the steam-bath with thionyl chloride (75 c.c.) for 30 minutes. Excess of thionyl chloride was removed under reduced pressure, and the residue distilled. 5-*Bromo*-o-*toluoyl chloride*, b. p. 136—138°/16 mm., was collected; it solidified to a mass of colourless plates (34 g.), m. p. 43° (Found: Cl, 30·1. C_8H_6OClBr requires Cl, 30·4%).

5-*Bromo*-o-*tolyl Diazomethyl Ketone*.—5-Bromo-*o*-toluoyl chloride (6·0 g.) in absolute ether was added to excess of diazomethane in absolute ether and left overnight. The solvent was removed under reduced

pressure and the residue crystallised from light petroleum (b. p. 40—60°). The *diazoketone* separated as yellow needles (3·7 g.), m. p. 83° (Found : N, 11·3. $C_9H_8ON_2Br$ requires N, 11·6%).

5-Bromo-o-tolylacetic Acid.—5-Bromo-*o*-tolyl diazomethyl ketone (34 g.) in dioxan (200 c.c.) was added with stirring to a suspension of silver oxide (4·0 g.) in a solution of sodium carbonate (9·8 g.) and sodium thiosulphate (6·4 g.) in water (400 c.c.) at 60°. The reaction was maintained at this temperature for 1 hour and then slowly raised to 90—100° and maintained at this temperature for a further 3 hours. The mixture was cooled, filtered, and extracted with ether. The aqueous layer was freed from ether, acidified with dilute nitric acid, the precipitate removed and crystallised from 20% aqueous alcohol, and the *acid* separated as colourless fluffy needles (21·0 g.), m. p. 116° (Found : Br, 34·2. $C_9H_9O_2Br$ requires Br, 35·0%).

cis-4-*Bromo-4'-cyano-2-methylstilbene-α-carboxylic Acid.*—Potassium 5-bromo-*o*-tolylacetate (11·2 g.), *p*-cyanobenzaldehyde (5 g.), pyridine (1 c.c.), and acetic anhydride (80 c.c.) were heated under reflux at 140—160° for 4 hours. The mixture was poured into water to decompose the excess of acetic anhydride, and the liquid extracted with ether (100 c.c.). The ether layer was separated, water (30 c.c.) added, and the liquid made alkaline with solid sodium carbonate; an oil then separated. The oil and aqueous layer were run off and cooled in ice. The sodium salt, when solidified, was collected, dissolved in hot water, and cis-4-*bromo-4'-cyano-2-methylstilbene-α-carboxylic acid* (9·9 g.) (50%) precipitated by acidification with hydrochloric acid. The acid crystallised from benzene–light petroleum as colourless prisms (6·2 g.), m. p. 178° (decomp.) (Found : N, 4·1; Br, 23·2. $C_{17}H_{12}O_2NBr$ requires N, 4·1; Br, 23·4%). The aqueous carbonate mother liquor from the above separation yielded on acidification a solid which crystallised from alcohol as colourless needles (0·7 g.), m. p. 260° alone and mixed with *p*-cyanocinnamic acid.

cis-4-*Bromo-4'-cyano-2-methylstilbene.*—(1) *cis*-4-Bromo-4'-cyano-2-methylstilbene-α-carboxylic acid (10·4 g.) was heated at 200—230° for 20 minutes and the residue distilled in a high vacuum over a free flame. The distillate set to a glass which was crystallised from ethyl alcohol; the *stilbene* separated as clusters of colourless needles (4·1 g.), m. p. 152° (Found : N, 3·9. $C_{16}H_{12}NBr,C_2H_5{\cdot}OH$ requires N, 4·0%).

Attempts to convert this into the *trans*-compound with iodine in nitrobenzene were unsuccessful, the original substance being obtained unchanged after 1½ hours under reflux.

(2) 5-Bromo-*o*-toluidine sulphate (4·75 g.) was dissolved in water (5 c.c.) and sulphuric acid (2·0 c.c.), and the whole diazotised with sodium nitrite (1·2 g.) in water (5 c.c.) at 5—10°. The diazonium sulphate solution was added with agitation to a solution prepared from *p*-cyanocinnamic acid (4 g.), sodium acetate (15·0 g.), and cupric chloride (0·10 g.) in acetone (100 c.c.) and water (20 c.c.) at 23—27°. Stirring was continued for 3 hours, and the mixture was then left overnight. The acetone was removed, the mixture shaken with benzene, and the benzene layer extracted with 2N-sodium carbonate. The benzene layer was dried and passed through alumina soaked in benzene and the column eluted with more benzene. The benzene eluate was again evaporated, the residue dissolved in light petroleum and adsorbed on alumina and eluted with light petroleum. The residue on removal of the solvent was crystallised from ethyl acetate and separated as colourless needles (0·1 g.), m. p. 152° alone and mixed with *cis*-4-bromo-4'-cyano-2-methylstilbene. The sodium carbonate mother liquid on acidification yielded unchanged *p*-cyanocinnamic acid (3·6 g.).

cis-4 : 4'-*Dicyano-2-methylstilbene.*—*cis*-4-Bromo-4'-cyano-2-methylstilbene (4 g.), cuprous cyanide (2·0 g.), and pyridine (2·0 c.c.) were heated at 200—210° for 1½ hours. A test attempt to extract the copper with hot concentrated hydrochloric acid resulted in hydrolysis of the cyano-group. Excess of pyridine was removed and the residue was distilled over a free flame in a high vacuum. The distillate was dissolved in benzene, passed through alumina and eluted with more benzene. The solvent was removed and the residue crystallised from ethyl alcohol; cis-4 : 4'-*dicyano-2-methylstilbene* separated in clusters of colourless needles (1·4 g.), m. p. 128° (Found : N, 11·3. $C_{17}H_{12}N_2$ requires N, 11·4%).

trans-4 : 4'-*Dicyano-2-methylstilbene.*—*cis*-4 : 4'-Dicyano-2-methylstilbene (0·8 g.) was heated in nitrobenzene (2·0 c.c.) with a trace of iodine for 30 minutes; dilution with light petroleum produced a white precipitate. This crystallised from alcohol, and trans-4 : 4'-*dicyano-2-methylstilbene* separated as colourless needles (0·7 g.), m. p. 208° (Found : N, 11·4. $C_{17}H_{12}N_2$ requires N, 11·4%).

trans-4 : 4'-*Diamidino-2-methylstilbene Dihydrochloride.*—*trans*-4 : 4'-Dicyano-2-methylstilbene (0·7 g.) in dry alcohol (25 c.c.) was saturated with hydrogen chloride at 0° and the mixture kept for 3 days. The voluminous precipitate of iminoether was filtered off and heated with alcoholic ammonia at 40° for 8 hours. The *amidine* crystallised from aqueous hydrochloric acid as light yellow prisms (0·5 g.), m. p. >360° (Found : N, 15·0; Cl, 19·1. $C_{17}H_{20}N_4Cl_2,H_2O$ requires N, 15·2; Cl, 19·1%).

cis-4 : 4'-Dicyano-2-methylstilbene treated in the above manner yielded only *trans*-amidine in poor yield (< 10%).

5-Bromo-o-toluoylhydrazide.—Methyl 5-bromo-*o*-toluate (23 g.), 50% aqueous hydrazine hydrate solution (35 c.c.), and ethanol (70 c.c.) were refluxed overnight. The mixture was cooled and *5-bromo-o-toluoylhydrazide* separated as colourless needles (21 g.), m. p. 160°. A small portion crystallised from ethyl alcohol for analysis had m. p. 163° (Found : N, 10·2. $C_8H_9ON_2Br,C_2H_5{\cdot}OH$ requires N, 10·2%).

Benzenesulphonyl-5-bromo-o-toluoylhydrazide.—5-Bromo-*o*-toluoylhydrazide (25 g.) in pyridine (260 c.c.) was cooled to and maintained at 0—5° while benzenesulphonyl chloride (30 c.c.) was added with stirring. Agitation was continued for 2 hours after the final addition of benzenesulphonyl chloride. The mixture was poured into excess of dilute hydrochloric acid and the crude product crystallised from alcohol; the *compound* separated as colourless needles (36 g.), m. p. 188° (Found : N, 7·6. $C_{14}H_{13}O_3N_2BrS$ requires N, 7·6%).

5-Bromo-o-tolualdehyde.—Benzenesulphonyl-5-bromo-*o*-toluoylhydrazide (4·8 g.) in ethylene glycol (30 c.c.) was heated to 160°, anhydrous sodium carbonate (3·6 g.) was added, and heating continued for 75 seconds. The mixture was diluted with boiling water, cooled, and extracted with ether. The solvent was removed, and the residue was shaken with an excess of saturated sodium hydrogen sulphite solution and left overnight. The aldehyde bisulphite was filtered off, washed with a little cold water,

and decomposed by warming on the steam-bath with dilute hydrochloric acid (100 c.c.). The liquor was extracted with benzene, separated, the solvent removed, and the residue distilled under reduced pressure. *5-Bromo-o-tolualdehyde* distilled as a colourless liquid, b. p. 95°/0·05 mm., n_D^{25} 1·5960; this solidified to a mass of colourless crystals (1·7 g.), m. p. 26° (Found: Br, 38·8. C_8H_7OBr requires Br, 40·0%). The *dinitrophenylhydrazone* crystallised from dioxan in clusters of orange needles, m. p. 256° (Found: N, 14·2. $C_{14}H_{11}O_4N_4Br$ requires N, 14·8%). The *semicarbazone* crystallised from glacial acetic acid as colourless prismatic needles, m. p. 228—230° (Found: N, 15·2. $C_9H_{10}ON_3Br,H_2O$ requires N, 15·3%. Found after drying: N, 16·2. $C_9H_{10}ON_3Br$ requires N, 16·4%). The *azine* obtained from the above aldehyde in 4% aqueous alcoholic hydrazine hydrate solution crystallised from glacial acetic acid as yellow needles, m. p. 176° (Found: N, 7·0. $C_{16}H_{14}N_2Br_2$ requires N, 7·1%). This compound sublimed unchanged in high vacuum.

4-Bromo-2-methylcinnamic Acid.—5-Bromo-o-tolualdehyde (2·5 g.), fused potassium acetate (1·7 g.), acetic anhydride (25 c.c.), and pyridine (1·0 c.c.) were heated at 140—150° for 6 hours. The mixture was poured into water, extracted with ether, and separated. The ether layer was extracted with 2N-sodium carbonate, separated, and the aqueous layer acidified. The precipitate was removed, dried, and crystallised from absolute alcohol. *4-Bromo-2-methylcinnamic acid* separated as colourless plates (0·5 g.), m. p. 208° (Found: Br, 33·1. $C_{10}H_9O_2Br$ requires Br, 33·2%).

cis-4 : 4′-*Dibromo*-2 : 2′-*dimethylstilbene-α-carboxylic Acid.*—Dry potassium 5-bromo-o-tolylacetate (14·0 g.), 5-bromo-o-tolualdehyde (10 g.), acetic anhydride (150 c.c.), and pyridine (3·0 c.c.) were heated at 140—160° for 4 hours. The mixture was poured into water and extracted with ether. The residue from evaporation of the ether extract was steam distilled to remove acetic acid, extracted with benzene, separated, and the benzene layer repeatedly distilled until the residue was dry. The gum was triturated with light petroleum (b. p. 80—100°) and the solid which deposited was filtered off. The residue was boiled with 2N-sodium carbonate, filtered hot, and the residue (0·25 g.) crystallised from glacial acetic acid. trans-4 : 4′-*Dibromo*-2 : 2′-*dimethylstilbene* separated as colourless prismatic needles, m. p. 182° (Found: Br, 43·7. $C_{16}H_{14}Br_2$ requires Br, 43·7%). The light petroleum solution was concentrated, and an intractable gum remained which resisted all immediate attempts at crystallisation. The residue was kept for three weeks; some solid had then been deposited. The residue was triturated with light petroleum (b. p. 80—100°) and filtered. This procedure was repeated thrice, and the solid fractions bulked together. This material was boiled with 2N-sodium carbonate (charcoal), filtered hot, and cooled. The solid which separated was removed, dissolved in boiling water, and the hot solution acidified with hydrochloric acid. The residue was removed, dried, and crystallised from light petroleum (b. p. 80—100°). cis-4 : 4′-*Dibromo*-2 : 2′-*dimethylstilbene-α-carboxylic acid* separated as colourless prisms (4·6 g.), m. p. 175° (Found: Br, 38·5. $C_{17}H_{14}O_2Br_2$ requires Br, 39·0%). The sodium carbonate mother liquors were acidified and the residue was crystallised from ethyl alcohol; m. p. 208° alone and mixed with 4-bromo-2-methylcinnamic acid (3·1 g.).

4 : 4′-Dibromo-2 : 2′-dimethylstilbene-α-carboxylic acid was heated at 170—200°/1 mm. The sublimate was removed and crystallised from light petroleum (b. p. 80—100°); m. p. 175° alone and mixed with starting material. The stilbenecarboxylic acid (1·0 g.) in quinoline (5 c.c.) with a trace of copper chromite was heated at 220° for 1½ hours. The residue was poured into hydrochloric acid and extracted with ether. No workable material was isolated even after chromatographic purification.

cis-4 : 4′-*Dicyano*-2 : 2′-*dimethylstilbene.*—*cis*-4 : 4′-Dibromo-2 : 2′-dimethylstilbene-α-carboxylic acid (3·2 g.), cuprous cyanide (2 g.), and pyridine (2·4 c.c.) were heated under reflux at 200—220° for 1½ hours. Excess of pyridine was removed and the residue sublimed at 200—260°/0·05—0·1 mm.; the sublimate was removed and crystallised from alcohol. cis-4 : 4′-*Dicyano*-2 : 2′-*dimethylstilbene* separated as colourless prismatic needles (0·6 g.), m. p. 166° (Found: N, 10·85. $C_{18}H_{14}N_2$ requires N, 10·85%).

trans-4 : 4′-*Dicyano*-2 : 2′-*dimethylstilbene.*—*trans*-4 : 4′-Dibromo-2 : 2′-dimethylstilbene (0·05 g.) from the above Perkin condensation, cuprous cyanide (0·05 g.), and pyridine (0·04 c.c.) were heated under reflux at 200—220° for 1½ hours. The residue was extracted with hot concentrated hydrochloric acid, and the solid recrystallised from nitrobenzene as colourless prisms, m. p. 272° alone and mixed with the product obtained by inversion of the above *cis*-4 : 4′-dicyano-2 : 2′-dimethylstilbene with iodine in-nitrobenzene.

trans-4 : 4′-*Diamidino*-2 : 2′-*dimethylstilbene Dihydrochloride.*—*trans*-4 : 4′-Dicyano-2 : 2′-dimethylstilbene (0·3 g.) in dry alcohol was saturated with hydrogen chloride at 0° and kept for 10 days. The residue (0·3 g.) was filtered off, treated at 40° with alcoholic ammonia for 8 hours, and the product crystallised from 5% aqueous hydrochloric acid. trans-4 : 4′-*Diamidino*-2 : 2′-*dimethylstilbene dihydrochloride* separated as colourless needles (0·28 g.) (Found: N, 14·5; Cl, 17·9. $C_{18}H_{22}N_4Cl_2,H_2O$ requires N, 14·6; Cl, 18·3%).

cis-4 : 4′-Dicyano-2 : 2′-dimethylstilbene treated in the above manner yielded only the *trans*-amidine in poor yield (10%).

The author wishes to express his indebtedness to Mr. S. Bance, B.Sc., for the several semimicro-analyses, to Dr. A. J. Ewins, F.R.S., for his interest, help, and encouragement, and to the Directors of May & Baker, Ltd., for permission to publish the results.

RESEARCH LABORATORIES,
MAY & BAKER LTD., DAGENHAM.

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NOTE.

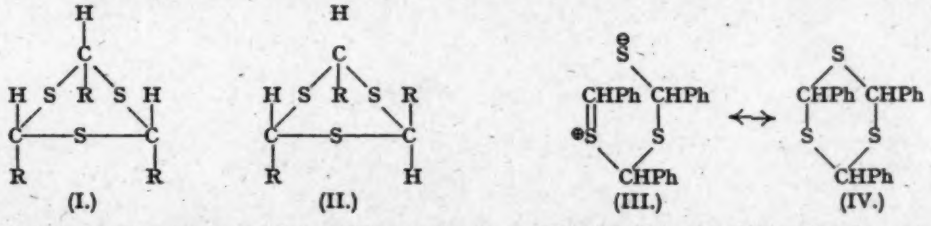
Organic Sulphur Compounds. Part XXX. The Stereochemistry of Trimeric Thioaldehydes. By ALEXANDER SCHÖNBERG and MOHAMED ZAKI BARAKAT.

THIOALDEHYDES are not stable as monomers, so very little is known about them; but many are known in trimeric form, *e.g.*, thioformaldehyde, thioacetaldehyde, and thiobenzaldehyde (Müller, *J. pr. Chem.*, 1927, **116**, 175; Baumann and Fromm, *Ber.*, 1889, **22**, 2600; *Ber.*, 1891, **24**, 1419, 1431, 1441). These are believed to be derivatives of 1 : 3 : 5-trithian (I; R = H), and their reactions agree with such a structure.

Some of the trimeric thioaldehydes have been prepared in only one form, but Wörner (*Ber.*, 1896, **29**, 139) enumerates sixteen which exist in two forms, known as α- and β-forms, the latter being the more stable.

According to Baumann and Fromm (*Ber.*, 1891, **24**, 1429), the existence of the two forms is due to stereoisomerism [compare (I) and (II)]. Some of the trimeric thioaldehydes are readily converted catalytically into their isomers; *e.g.*, trithioanisaldehyde, m. p. 127°, is changed into its isomer, m. p. 183°, in less than a minute on treatment of its solution in benzene with a few crystals of iodine at room temperature, and the change of α- into β-trithiobenzaldehyde is almost as rapid (Baumann and Fromm, *loc. cit.*, pp. 1441, 1435). When α-trithiobenzaldehyde is treated with acetyl chloride, crystals of the β-form begin to separate before the α-form is completely dissolved (Suyver, *Rec. Trav. chim.*, 1905, **24**, 400). The α-form of trithioacetaldehyde is converted into the β-form at room temperature in the presence of traces of iodine (*idem*, *ibid.*, p. 387).

These ready changes of trimeric thioaldehydes from one isomer to the other seem to us not to be in accordance with Baumann and Fromm's hypothesis. In the cyclic series interconversion of *cis-trans*-isomers takes place *readily* only when there is a possibility of tautomerism, *e.g.*, with menthone and camphoric acid (Shriner, Adams, and Marvel in Gilman's "Organic Chemistry," New York, 1938, p. 399; Wagner-Jauregg in Freudenberg's "Stereochemie," Leipzig and Vienna, 1932, p. 860); but with the compounds in question there is no such possibility. Current theory demands that in molecules such as (I) and (II) the ring structures do *not* restrict the freedom of rotation around the single



bonds between the atoms of the ring (Gilman, *op. cit.*, p. 395), but it is evident that there is no justification for such an assumption, so, in order to support Baumann and Fromm's stereochemical conception, one would have to assume that the catalyst may cause reversible depolymerisation and thus bring about the observed change of one form into the other. This would be an *ad hoc* hypothesis without experimental evidence, for the 1 : 3 : 5-trithians are stable even to strong alkalis and acids.

To explain the existence of α- and β-forms of trimeric thioaldehydes and the ready conversion of the former into the latter, the following theory is advanced. The three carbon atoms and the three sulphur atoms in these 1 : 3 : 5-trithian molecules do not lie in one plane, but may be regarded as "boat" and "chair" structures, the interconversion then being readily explained. According to this explanation, the α- and the β-form of trithioacetaldehyde, for example, are either both *cis*- or both *trans*-forms; the isomeric change is due to a change of the "boat" into the "chair" structure or *vice versa*. This new theory demands a greater number of isomers than have, so far, been isolated, but it is not thereby necessarily invalidated, for other isomers (γ-forms) have occasionally been described, which have been attributed *inter alia* to polymorphism or the occurrence of eutectic mixtures.

In harmony with the new theory is the fact that the molecule of trithioformaldehyde in benzene solution and in the crystal contains, not a planar but a puckered six-membered ring (Sachse's chair ring) (Moerman and Wiebenga, *Z. Krist.*, 1937, **97**, 330).

The "chair" and the "boat" form of *cyclo*hexane have not been isolated, but the *cyclo*hexane and the 1 : 3 : 5-trithian ring system differ, the latter but not the former being capable of resonance, (III) ⟷ (IV) (only two resonating structures are drawn), so the two possible forms of *cyclo*hexane and its simple derivatives are not stabilised by resonance.

The similarity between the *cyclo*hexane ring and the trithian ring which is frequently stressed is only formal, in contrast to the real similarity between the thiophen and the benzene ring. This may be seen from a comparison of the m. p.s, benzene (5·5°), thiophen (−30°), *cyclo*hexane (6°), and trithioformaldehyde (215°).—FOUAD I UNIVERSITY, ABBASSIA, CAIRO. [*Received, October 24th*, 1944.]

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Some Observations on Present Day Chemical Kinetics.

By C. N. HINSHELWOOD, M.A., Sc.D., F.R.S.

IN what follows I propose to make some observations upon certain aspects of chemical kinetics. These relate not so much to details of recent advances as to the general structure of the subject, which, like everything else, is gradually changing.

The study of kinetics in its earliest stages was, one may suppose, stimulated by the fascination which exists in surveying the unfolding of phenomena in time. In a slow chemical reaction a sort of microcosm of history evolves as it were before our eyes, and it is not surprising that the first of all objects was to find and interpret the law according to which the amounts of substance changed with time. The law of mass action and the conception of reactions of different orders, based upon the theory of probability, seemed to give a satisfactory explanation of what occurred and to offer a basis for a rational classification of reactions. But we have seen this idea sadly disappointed, and today it must be recognised that from the point of view of concentration–time relationships chemical kinetics seems sometimes to present a picture of almost forbidding complexity. Yet the very reason for this at first sight discouraging result lies in a circumstance which itself is gradually leading to major simplifications and generalisations of a different kind. It has transpired that most reactions take place in a series of stages: it appears that many are chain reactions. They are chain reactions because the intermediates are free atoms or radicals, that is to say entities which have been formed by the primitive process of severing a bond. Now what the studies of many experimenters have combined to show, and what several authors have been at pains to point out in individual cases in detail, is that, even in non-chain reactions, the sequence of steps by which most reactions accomplish themselves is one in which each successive member is of extreme simplicity, involving, for example, the reaction of the fewest molecules, the breaking of a single bond, or the transfer of a single atom or electron from one reacting partner to another.

This seems to open up a possibility of some magnitude, namely that the work of these various authors may be generalised and that we may presently be able to formulate rules, based upon our general knowledge of structure and properties, and according to which, looking at a given complex reaction, we shall be able to predict what in fact constitutes the simplest series of steps into which it should be resolved. Once this is done the whole kinetic scheme can be worked out from first principles. This subject at any rate seems to constitute a very fruitful field of enquiry at the present time. In this connexion I might refer to the discussion by Evans (*Trans. Faraday Soc.*, 1944, **40**, 120) of the action of nitric acid on metals which gives a good idea of the way in which order may be brought out of chaos. Following this general idea I have tried in another lecture to show that even the manifold and at first sight mysterious phenomena exhibited by the hydrogen–oxygen reaction are, in the light of modern ideas, almost if not quite predictable from first principles (*Proc. Roy. Soc.*, 1946, *A*, **188**, 1).

We are witnessing the gradual emergence of a new kind of classification of chemical reactions. It may be worth while to consider this briefly from a very general point of view. Spontaneous changes proceed with diminution of free energy; but if they are of the kind whose progress can be measured there are nearly always energy barriers separating the initial and the final states. The overcoming of these barriers depends upon strong local fluctuations whereby one or both of two things may happen: (*a*) abnormal amounts of energy are accumulated in a few molecules, and (*b*) there is a momentary occurrence of unusual spatial distributions of molecules. If a great deal of energy has to be concentrated locally we speak of a high energy of activation: if many molecules have to come together, or if they need to assume highly specialised positions and orientations, then we speak of a low entropy of activation. Both of course represent entropy decreases from the point of view of the system as a whole.

The first major division of reactions depends upon whether this local fluctuation is dissipated after a single act of chemical transformation, or whether its effect persists through a series of such acts so as to give rise to a chain reaction. The commonest form of such reactions involves a succession of steps each with a high entropy of activation. And the overall kinetics are affected more perhaps by the mode in which the dissipation of the original fluctuation occurs—that is, by the mode of chain breaking—than by any other factor.

In the pyrolysis of organic compounds striking differences in kinetics arise from the different modes of radical re-combination (for example, in the decomposition of ethers, whether two

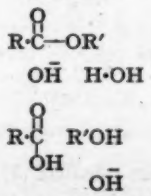
light radicals, or a light and a heavy one, combine). In the important class of reactions in which successive steps of the chain build up polmeric molecules of increasing size, the whole kinetic classification depends essentially upon the mode by which the chains are ended, and in the detailed study this usually constitutes one of the main problems to be solved. It has been the subject of close analysis by Flory, Melville, and others and now constitutes almost a separate chapter of physical chemistry. In most chain reactions what persists is the effect of the original local energy fluctuation—that is, an effect connected with the activation process. A persisting effect of a low entropy of activation is a characteristic of the reactions of living matter, a topic to which I shall return presently.

To turn, however, to those reactions in which the initial energy fluctuation does not persist—that is, to non-chain reactions—it is obvious that if they were in fact all reduced to the simplest possible form, even they would consist of sequences involving at each step only the breaking of a single bond, the transfer of a single atom, or a simple flow of electrons. But the energy conditions would usually be very unfavourable. The energy barriers are lowered when suitable receptor molecules are present and suitably disposed to take up atoms or radicals released by the breaking of bonds, and when suitable complexes are formed which obviate the need for the appearance of unnatural charges on atoms. But these conditions inevitably demand precisely defined and specialised configurations at the moment of reaction—that is to say, greatly lowered entropy of activation. In the same way the unfavourable energy conditions attending the reaction of particles bearing like charges are improved when these charges are screened by the presence of suitable ions (as exemplified by the salt effect) : but here again the need for extra particles in the transition state introduces an unfavourable entropy factor. The antagonism of the energy factor and the entropy factor dominates the whole of the phenomena of kinetics, and one of the great needs, if a satisfying edifice of theoretical chemistry is to be constructed, is for the rules governing the balance to be formulated in a clearer way than has hitherto been possible.

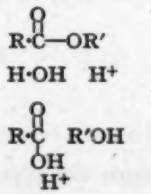
Among the consequences of this antagonism is the change of mechanism which is sometimes observed at a certain point in a related series of reactions. The well-known example is the hydrolysis of the alkyl halides, which changes from a bimolecular to a unimolecular mechanism as the nature of the alkyl radical is varied (cf. Hughes, Liversidge Lecture, *J.*, 1946, 968). Such a change of mechanism with relatively small changes in the reactant would be likely only if the advantage which one mode possessed over the other were rather nicely balanced.

Without actually revealing changes of mechanism, series of reactions in which one reactant is progressively changed by the introduction of substituents not infrequently show parallel increases of activation energy and of the non-exponential term, *i.e.*, as the energy factor becomes less favourable to reaction the entropy factor in compensation becomes more favourable. When a high degree of activation is required the configuration at the moment of transition needs to be less precisely defined than when a low degree of activation is needed. In a general qualitative way this can be understood, but more detailed knowledge is desirable about the conditions which determine when this phenomenon is observable and when, on the other hand, changes in the rate are determined wholly by the change in activation energy. One example only need be mentioned. In the alkaline hydrolysis of benzoic esters, changes in the substituent cause changes in rate wholly accounted for by changes in the activation energy. In the acid hydrolysis of esters and also in the acid catalysed esterification reaction there is a marked compensation of the energy and the entropy terms. The alkaline and acid hydrolysis reactions may be formulated as follows :

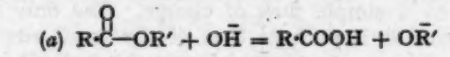
Alkaline.

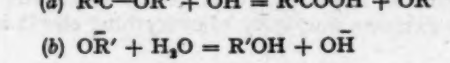


Acid.



The chief resistance to reaction is represented by the energy required to bring the hydroxyl ion or the water molecule up to the carbonyl carbon. This energy is less with the hydroxyl ion, and one might suppose the reaction to approximate to the two stage process :





(*b*) being rapid compared with (*a*). If this is so, the orientation and distance of the water molecule become irrelevant, and the only influence of changes in R is on the energy term. In acid hydrolysis the water molecule is a much less active agent, the activation energy is greater, and the co-operation of the hydrogen ion is required. Furthermore, we might suppose the link between the carbonyl carbon and the alkoxyl group to weaken in different degrees according to the magnitude of the repulsion overcome by the approaching water. If this repulsion is great, the transition state may well be attained when the water is at a greater distance than when the repulsion is weaker; the entropy of the transition state is thus greater, and compensates to some extent the more adverse energy. This idea involves an assumption which may be stated in more general terms as follows. In a transition state *A B C* a given weakening of the bond *BC*

$$A \;.\;.\;.\;.\;.\;.\;.\;B\text{----------}C$$
$$\qquad\quad r_1 \qquad\qquad r_2$$

caused by the approach of *A* will have occurred at a greater value of r_1 when the repulsion of *A* by *B* is large, than when it is small. Whether or not this idea is sound (though it seems plausible) is difficult to say, but what is certain is that a series of propositions of this kind based upon theoretical studies of bond energies and their variations would be of the greatest help in systematising kinetic phenomena still further. This is a developemnt to which we must look forward in the decade before us.

I should like to consider briefly a few typical chemical reactions with the object of considering how far we are able to imagine which is the simplest possible series of steps into which they can be resolved, subject always to the condition that the best balance between the entropy and the energy factors is achieved. This discussion must at the moment be a good deal less systematic than one would like, but it may serve to reveal some of the ways in which order is gradually emerging.

Certain reactions of the halogens will first serve for the present purpose. A reaction to which a great deal of patient study has been devoted (Griffith, McKeown, and Winn, *Trans. Faraday Soc.*, 1932, **28**, 107) is the oxidation of oxalic acid by bromine. It transpires that the complicated rate–concentration relations can be well accounted for by the assumption that the rate is proportional to

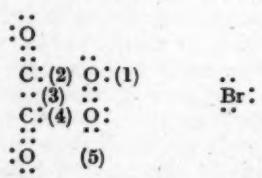
$$[HC_2O_4^-]\,[HBrO]$$

The usual conclusion would perhaps be that the two molecular species here represented are those between which the determinative reaction step occurs. The process by which these two structures yield carbon dioxide, bromide, and water involves, however, several simultaneous events which do not look so natural and inevitable as to seem those which would be predicted from first principles. It is of some interest to pursue here the idea of maximum simplicity and to see to what it leads. Halogens are to some extent amphoteric, and a small dissociation of bromine according to the equation

$$Br_2 = Br^- + Br^+$$

is very likely, and involves no more than an electron redistribution. The cross equilibria which are immediately established in aqueous solution between Br^- and H^+ and between Br^+ and OH^- give at once, and in the most natural way, the bromine–bromide–hypobromite equilibrium.

We may now consider the behaviour of the positive bromine ion when it encounters the oxalate ion $C_2O_4^{--}$.



If a positive bromine ion approaches the electron pair labelled (1) in the diagram it can remove them and become a negative ion, $:\ddot{Br}:$, with a complete octet. Electron pair (3) now joins pair (2) with rupture of the bond between the two carbon atoms and formation of the double bond of CO_2. Then pair (5) joins pair (4) and the second molecule of CO_2 is formed, the whole process amounting to a simple flow of charge. The only step here which may be objectionable on energy grounds is perhaps that of the small amphoteric ionisation of the halogen, but in view of the extreme simplicity of everything else it is tempting to assume it.

However this may be, the scheme I have outlined, even if it does not correspond to reality, exemplifies the type where the various entropy of activation terms are the greatest possible. It is easily shown that reaction of positive bromine with oxalate ion leads to precisely the kinetic scheme referred to above.

Arguments have been adduced (J. C. Morris, *J. Amer. Chem. Soc.*, 1946, **68**, 1692) to show that the hydrolysis of chlorine is best explained by the mechanism $Cl_2 + \bar{O}H = HOCl + Cl^-$. This may be a stage easier from the energy point of view, and is a stage more difficult from the point of view of entropy.

The oxidation of arsenious acid by iodine also exhibits rather complex kinetics, but these have been shown to depend upon the control of the key concentrations by various subsidiary equilibria. The observed rate seems to be governed by the bimolecular action of H_3AsO_3 and HIO giving H_3AsO_4 and HI. Here we have a simple atomic transfer, which, in view of the formulæ of the two arsenic compounds, is again seen to be from the entropy point of view among the least elaborate processes possible.

Perhaps in contrast with the above we might consider the reaction by which phenols are iodinated. According to the work of Li (*J. Amer. Chem. Soc.*, 1942, **64**, 1146) and of Soper and Smith (*J.*, 1927, 2757) the relation between the reaction rate, the pH, and the various concentrations indicates the mechanism by which the molecule HOI reacts both with ϕOH and (much more readily) with $C_6H_5O^-$. If we wished here to postulate I^+ as one reactant it would be necessary, to preserve the form of the kinetic equations, to assume $C_6H_4{}^-O^-$ as the reaction partner—that is, to suppose that the replaceable proton of the aromatic compound ionised in a separate step. There are of course serious objections to this view. Thus, what seems to be preferred is, in this case, not

$$\rangle C - H \longrightarrow \rangle C^- + H^+$$
$$\rangle C^- + I^+ \longrightarrow \rangle C - I$$

but

$$\rangle C - H + I^+ - OH^- = \rangle CI + H_2O$$

In other words the positive iodine ion prefers to react with its hydroxyl attached, rather than free, in order that the proton may be duly removed and accommodated. Now this process involves two simultaneous operations instead of a single one. It is therefore less favourably placed from the point of view of the entropy change. On the other hand, the formation of water gives an important compensation in the energy term. Here it must be admitted that an attempt to predict the course from first principles would encounter an ambiguity, only resolvable with the aid of more satisfactory theoretical propositions about bond energies, which once again appear as one of the greatest desiderata in the subject.

Another interesting reaction of the halogens is the haloform reaction. In this the overall change appears to be of some complexity. But it is known, on the one hand, that under suitable conditions mono-, di-, and tri-halo-ketones can be formed: and on the other hand, it has been found that the reaction may be of zero order with respect to the halogenating agent and of the first order with respect to the ketone and to hydroxyl ions (Bell and Longuet-Higgins, *J.*, 1946, 636). These facts point to the steps:

$$R{\cdot}CO{\cdot}CH_3 + OH^- = R{\cdot}CO{\cdot}CH_2^- + H_2O$$
$$R{\cdot}CO{\cdot}CH_2^- + X^+ = R{\cdot}CO{\cdot}CH_2X$$

and then two repetitions of similar reactions till $R{\cdot}CO{\cdot}CX_3$ is formed. For the final stage we have the alternatives

$$R{\cdot}CO{\cdot}CX_3 = R{\cdot}CO^+ + CX_3^-$$
$$R{\cdot}CO^+ + OH^- = R{\cdot}CO{\cdot}OH \text{ and } CX_3^- + H^+ = CHX_3$$

or

$$R{\cdot}CO{\cdot}CX_3 + HO{\cdot}H = R{\cdot}CO{\cdot}OH + CHX_3.$$

In all this we see that the rational classification of the reactions is somewhat as follows:

(1) Internal re-distribution of electrons with breaking of a bond and the appearance of a charge, or of a free bond in a new place.

(2) Transfer of charge from one atom or molecule to another.

(3) Transfer of an atom from one molecule to another.

(4) Exchange of partners according to the scheme

$$\begin{matrix} A{-}B \\ X{-}Y \end{matrix} = \begin{matrix} A & B \\ | & | \\ X & Y \end{matrix}$$

These represent a series in which the requirements in the way of low entropy of activation progressively increase. Many reaction steps can be classified under one or other of these headings. In time we hope to be able to predict which sequence is appropriate to any given case.

Another principle which helps in interpreting the mass of facts is that, in general, reactions will occur between uncharged molecules, an uncharged molecule and an ion, or oppositely charged molecules, in preference to reactions between molecules of like charge. Let us consider what is likely to happen when hydrogen bromide reacts with bromic acid to give bromine. In the first place reaction is more likely to occur between the ion pairs H^+Br^- and $H^+BrO_3^-$ than between Br^- and BrO_3^-. When the ion pairs meet, the simplest reaction is the transfer of a single atom of oxygen from one to the other giving HBrO and $HBrO_2$. The latter must be very unstable and will at once react again with HBr with a further single atom transfer giving 2HBrO. HBrO and HBr then of course react immediately to give bromine and water. The rate-determining step would seem then to be governed by the product: ion pair H^+Br^- × ion pair H^+BrO^-, which is roughly proportional to $[H^+Br^-]$ $[H^+BrO_3^-]$ or $[H^+]^2$ $[Br^-]$ $[BrO_3^-]$, giving the well known fourth order reaction commonly measured.

In a somewhat similar way the reaction between nitrite and iodide in acid solution is known to be approximately of the fourth order $[NO_2^-]$ $[I^-]$ $[H^+]^2$ which is most simply interpreted as [ion pair HNO_2] [ion pair HI]. These pairs suffer the partner-exchange type of reaction $\begin{matrix}ON-OH\\I-H\end{matrix} = H_2O + NOI$, the NOI being unstable and breaking down at once, as would be expected from the known properties of NOCl and NOBr, to give nitric oxide and iodine.

For some purposes it would be convenient to regard salt effects on reaction velocity from this same point of view. The well-known result that reactions between like ions are accelerated by increases in the total ionic strength and those between unlike ions retarded is susceptible, as one knows, to a semi-thermodynamic treatment in terms of the activity coefficients of reactants and transition complex. From a purely kinetic point of view one can refer the effect to the greater probability of reaction between uncharged ion pairs AX and BY than between the charged ions X^- and Y^-. There are few things which would be of greater assistance in kinetics than a simple approximate and manageable theory of ion pair formation and it is to be hoped that one will some day be forthcoming.

If the theory referred to is lacking, valuable work is being done on the formation of complex ions in solutions of metallic salts. The realisation that these may often be the major participants in reactions facilitates the simple formulation of many changes. To take an example, the reaction which used to be formulated

$$2Fe^{+++} + Sn^{++} = 2Fe^{++} + Sn^{++++}$$

seems on good evidence (Weiss, *J.*, 1944, 309) to proceed by the stages

$$SnCl_2 + 2Cl^- = SnCl_4^{--}$$
$$SnCl_4^{--} + Fe^{+++} = Fe^{++} + SnCl_4^-$$
$$SnCl_4^- + Fe^{+++} = Fe^{++} + SnCl_4$$

Two principles are satisfied here, namely, that reactions should preferably occur between particles which do not bear like charges, and that electron transfers occur in simple unit steps.

The kinetics of the nitration of aromatic compounds presents at first sight many complexities. These have recently been unravelled, and it now appears that they can be explained very satisfactorily by the assumption that the NO_2^+ ion is produced. This by the simplest possible exchange process replaces the proton on the negative reaction centre in the benzene ring.

In sulphonation by sulphur trioxide it seems that the molecule S_2O_6 may be involved: in the halogenation of unsaturated compounds, molecules such as Br_4 are indicated by the work of Robertson. The prior equilibria in which entities such as Br^+, Br_4, S_2O_6, NO_2^+, $Fe^{++}Cl$, $SnCl_4^{--}$, and so on participate now appear to be of the greatest interest. They present us (as do the various ion pairs referred to above) with particles by whose reaction apparently complex acts may be performed in single encounters where the entropy of activation is not impossibly low.

A new inorganic chemistry of such equilibria is now due, in which the theory of structure will become more closely linked than ever to the theory of kinetics. The latter has, so far, often taken the lead in indicating the existence of unexpected species in small concentration (for example, N_2O_2, S_2O_6, and so on) but perhaps the compliment may now be returned and a more careful study of the inorganic chemistry of unstable species may help us to predict the most probable kinetic mechanisms in examples as yet unexplored.

Other striking examples of the way the tendency to maximum simplicity operates are to be

found in the consideration of Rice and Teller and of Rice and Kossiakoff concerning the sequence of steps in chain reactions of organic compounds. These considerations help us appreciably along the road towards the prediction of the most likely sequence of changes.

To sum up certain indications from what has been said so far, I think the time is ripe for a considerable forward movement in structural inorganic chemistry, which will be brought into closer and closer relation with kinetics. The establishment of a series of workable qualitative propositions about bond strengths, and the development of a manageable approximate theory of ionic interactions, would further this work in a spectacular manner.

Time is lacking for any detailed discussion of heterogeneous reactions, but I should like just to say a word about their place in the general scheme of things. The essential thing is that the formation of chemical links between surface atoms and adsorbed atoms or radicals allows the resolution of reactions into steps of maximum simplicity with lowered energy barriers. An important character is that the active intermediates, instead of being free and transient, are preserved, as it were, in a state of suspended animation, until the appropriate reaction partners arrive. More and more progress is made in formulating the changes of heterogeneous catalysis by definite chemical equations. I will mention in passing only one example which is of a somewhat surprising kind. Eucken and Wicke (*Naturwiss.*, 1944, **32**, 161) found that, paradoxically as it at first appears, the dehydration of *iso*propyl alcohol by alumina demands the presence of water on the catalyst surface. They interpret their experimental findings by the following scheme :

Initial. Final.

The hydrogen atom virtually migrates from one oxygen atom of the catalyst to the next : though what actually happens is that the catalyst itself contributes an atom of hydrogen to the water eliminated and receives one from the alcohol.

Much progress has been made in ordering chemical kinetics into a finished system : much remains to be done. The stages of many reactions, such as oxidation reactions of organic substances, are by no means understood ; the interplay of energy and entropy factors needs further elucidation ; the inorganic chemistry of ionic complexes needs elaboration ; a simple and manageable approximate theory of ion pair formation is desirable ; a series of qualitative propositions about the interatomic forces involved in activation phenomena needs to be formulated. Much more information about the nature of intramolecular energy transfers may be expected to be forthcoming. All these potential advances are, however, of the nature of perfecting operations applied to an edifice the general structure of which is already evident. We think we know—though it is as well to be prepared for possible surprises—the general form of the phenomena which will be observed and of the explanations which will be provided for them. If we may appropriate from another field of scholarship the distinction of " classical " and " romantic ", then the advances to be made in the parts of the subject I have just been talking about belong essentially to the " classical " : the " romantic ", in the sense in which I am taking it, lies in the direction of those phenomena which are still mysterious and where not only the precise form but even the general character of the findings and of their explanations is largely unknown.

I have the feeling not only that such a region lies where chemical kinetics is applied to the living cell, but that the time is ripe for its further exploration. Some people doubt whether much progress can be made in this direction, and they may of course be right. But in many ways the transition from the kinetics of the systems we normally study to those of the cell is a quite natural one, and I do not share this negative belief.

If we consider the classification of reactions of the inorganic world we see a steady transition to those of the living cell. The resolution of a complex change into a series of simple stages is familiar ; the appearance of transitory free atoms and radicals is well known ; the study of polymerisation reactions has made us familiar with the continuous building up of large molecules by repeated additions to a persisting free radical ; in reactions where solid products are formed we have the reproduction of basal patterns of molecules by steady additions of fresh units. In the reactions of a living cell we seem to have a combination of all these processes. And the new problem presented to kinetics is that of the mode of their interplay.

In the cell there is a highly ordered macromolecular pattern. Its order constitutes an element of low entropy—that is, it is something inherently improbable. This is reflected in an interesting way in the kinetics of denaturation of proteins. The denaturation process has a very high activation energy (which shows that the ordered structure has a considerable element of stability), but the non-exponential factor is extremely high. In other words, the entropy of activation is high, showing that the transition state is much less ordered—that is, more probable—than the initial state. The intact protein must therefore have been highly ordered, even though energetically fairly stable. This will apply to the cell material as a whole.

The process of self-synthesis proceeds in a manner which bears some analogy with crystal growth, the existing pattern guiding the new molecular units into suitably ordered positions. The entropy of activation for this synthetic process is not impossibly low, precisely because there is a persistent structure of low entropy (low probability) continuously maintained in the self-reproducing, ordered pattern. The original fluctuation which may have permitted the emergence of this order does not dissipate itself as in ordinary chain reactions, but is preserved for all time, provided that the cell mechanism continues to function. But the low entropy systems are being continually enlarged, and this is only possible if there is a steady and compensating running down of free energy. This occurs in the oxidation and other degradative reactions which accompany the autosynthetic reactions of the cell.

How one set of processes which involve increase of entropy can balance another set involving decreases is a matter which at first sight seems mysterious, but which, in principle at least, is seen to be simple when the resolution of reactions into stages is borne in mind. The following scheme shows how the coupling is in principle possible. The sequence

$$A_2 = A + A$$
$$A + XY = AX + Y$$
$$AX + B = AB + X$$
$$AB + A = BA_2$$

is equivalent to

$$(1)\ B + A_2 = BA_2$$
$$(2)\ XY = X + Y$$

If (1) proceeds with diminution of free energy it pays the way, as it were, for (2) which can proceed with increase of free energy.

The reactions of the cell which release free energy are those such as oxidation. Oxidation reactions are almost certainly chain reactions producing free radicals. But in contrast with what happens, for example, in a mixture of hexane vapour and oxygen, these free radicals are not subject to rapid dissipation processes, because they are preserved from decay by their attachment to the more or less rigid macromolecular structure of the cell material. Cells may remain alive for a time at least without growing, and then they preserve their free radical ends in a state of mobilisation until suitable substrates are presented for them to react with. The cell, in simplest terms, consists of macromolecular polyfunctional free radical systems, constituting a region of low entropy (in virtue of its order) and low energy of activation (in virtue of its free valencies) and persistent (in virtue of its relatively rigid structure).

The system itself is thus a combination of elements with which we are already familiar in the ordinary kinetics of homogeneous and heterogeneous reactions: the mystery consists in the way in which these elements are combined so as to give rise to the phenomena of cell activity.

I should like therefore to refer briefly to the way in which one or two cell phenomena admit of discussion in terms of chemical kinetics.

One of the most remarkable manifestations of the power of the living cell is the phenomenon of adaptation. Many bacterial cells placed in presence of a new source of material, such as a new sugar for a carbon supply, are unable at first to utilise it with maximum efficiency, but learn, as it were, to do so on continued growth in the medium. Bacteria, moreover, grown in presence of an antibiotic drug at a concentration which is not completely inhibitory, often—one might even say usually—acquire a resistance to its action, and this resistance may be developed to such a degree that completely normal growth can occur in presence of concentrations a hundred times or more greater than that which would originally have stopped all growth. The most obvious explanation of these phenomena might seem at first sight to be a purely biological one, namely that the bacterial strains consist from the start of cells with different capabilities, some for example able to utilise the new substrate, others naturally resistant to the drug, and so on, and that the adaptive process consists in the selection of those cells most capable of flourishing in the new environment. Numerous detailed studies seem, however, to show that this explanation is inadequate and that there must be actual changes in the cell,

called forth by those conditions to which the adaptation occurs. These changes must consist either in the establishment of a new quantitative balance of the enzymes in the cell, or in an actual modification of the protein texture of the cell material. The adaptations show complex phenomena of reversibility or non-reversibility according to conditions, consistent with this idea, which is supported by many arguments into which I shall not enter here.

Where there is a change in the enzyme balance of the cell a direct application of kinetic ideas becomes not only possible but imperative. The synthetic reactions of the cell must consist of many stages; in the steady state of growth the rates of the different steps are so adjusted that the various parts of the cell material are built up in a standard ratio. Changed conditions may affect in unequal degrees the various synthetic reactions. This will be specially true of certain drug actions, which according to the Fildes theory are extremely specific in respect of the site of attack. When the relative rates of the different steps are changed, the proportions of the cell enzymes built up must also change, and this will lead to a calculable alteration in certain biochemical properties, such as the drug resistance. The theories which have been developed on this basis are as yet in a rough and ready state, and no doubt contain gross faults, but there can be little doubt that general propositions based upon the theory of consecutive reactions have much to say about the phenomena of cell adaptation. Thus one of the very characteristic properties of living matter comes naturally within the purview of chemical kinetics.

Not only changes in enzyme proportions, but also qualitative modifications of the protein or other macromolecular texture, must be considered and are of great importance in connexion with the theory of mutations and of adaptive processes. There seems little doubt that in the reproduction of cell material the deposition of new substance is guided by the pattern of the old in a way which is at least in part analogous to crystal growth. The possibility of forcing an initial change of pattern by the incorporation, for example, of some fresh foreign units into the macromolecular texture, will depend upon the energy and entropy of activation. These may vary greatly, and, according to their values, there may be all gradations of phenomenon between an apparently discontinuous mutation and a gradual reversible adaptation.

These matters are accessible to experiment in many ways: for example, growth in presence of one sugar may retard or even reverse the adaptation to another (Monod, " La Croissance des Cultures Bactériennes ", 1942; Postgate and Hinshelwood, *Trans. Faraday Soc.*, 1946, **42**, 45); growth in presence of ammonia–asparagine mixtures trains bacteria, which are initially unable to utilise ammonia alone, to perform this operation; the chief requirement for the adaptation of certain bacteria to *d*-arabinose (which they are initially unable to utilise) is the lapse of sufficient time in presence of this sugar—growth in mixtures of *l*-arabinose and *d*-arabinose being moreover no more effective than growth in mixtures of glucose and *d*-arabinose (G. A. Morrison, S. Jackson, unpublished observations). Systematic collection of observations of this kind and careful thought about their interpretation can hardly fail to contribute to our enlightenment about the nature and mode of incorporation of the molecular fragments which cells use in their synthetic operations, and about the manner of their functioning.

Another group of observations of which the interpretation constitutes a characteristically kinetic problem is that where one set of cell reactions is, in the most remarkable way, inhibited and superseded by another set. In the well-known Pasteur effect provision of oxygen inhibits the fermentation reactions by which the cell obtains its energy under anærobic conditions. Provision of oxygen in the growth of *Bact. lactis ærogenes* lessens the reduction of nitrate and nitrite; and supply of ammonia for growth inhibits the consumption of nitrite for that purpose (P. R. Lewis, unpublished observations). In all these examples it appears at first sight as though the cell knew how to select the more profitable of two alternatives: and yet such phenomena can be interpreted in terms of the rise or fall in the transient stationary concentrations of certain intermediates as the conditions of the reaction change.

There is not time for a detailed discussion of these matters, and I pass to a concluding observation. Kinetic studies (in the broadest sense of the term) have a definite contribution to make to the understanding of cell phenomena, but naturally they cannot stand by themselves. The work of Stacey and the Birmingham school on the polysaccharide components of micro-organisms (Stacey, Tilden Lecture, 1946), work on immunity, on the *X*-ray structure of proteins, on the organic chemistry of the nucleotides and so on, are in many ways more direct and more important modes of attack. And yet it is only by studying function that we can understand function, so that the kinetic aspect must be allowed to retain its place and assigned its part in the unravelling of the great mystery.

ONE HUNDRED AND SIXTH ANNUAL GENERAL MEETING.

The One Hundred and Sixth Annual General Meeting was held at 12 noon on Thursday, March 20th, 1947, at the Rooms of the Chemical Society, Burlington House, W.1, the President, Professor C. N. Hinshelwood, in the Chair.

The notice convening the meeting was read.

Before the Report of Council was presented for adoption, the meeting on a motion by the President adopted a resolution placing on record the Society's regret at the death of Dr. Alexander Scott, a Past President, the text of which reads as follows :

> " The President, Council and Fellows of the Chemical Society learned with profound regret at their meeting to-day of the death on March 10th of their distinguished Past President, Dr. Alexander Scott. They desire to express their high appreciation of his contribution to the Science of Chemistry and to record their indebtedness to him for his devotion to the affairs of the Society. He was a Fellow of the Society for sixty-eight years and was first elected a member of Council in 1897. He became Honorary Secretary in 1899, Treasurer in 1904 and President in 1915. Following his Presidency, Dr. Scott continued to serve the Society as Vice-President from 1917 to 1928 and again from 1930 to 1933.
>
> The Society conveys its deepest sympathy to Mrs. Scott in her great sorrow."

In presenting the Report of Council for 1946, copies of which were available, Dr. Simonsen referred to the increase in the number of papers published during the year and the increase in the size of the *Journal*. He paid tribute to the Society's printers for their co-operation in the face of the very considerable difficulties which confront them. The Council was mindful of the large number of papers awaiting publication, and it was its constant endeavour to have these published as soon as paper and labour shortages could be overcome.

He referred also to the activities of the Publication Committee and the Editor in preparing two publications not mentioned in the report, the *Quarterly Reviews* No. 1 which would be issued in the very near future and the *Annual Reports* for 1946 which were in an advanced state of preparation.

Dr. Simonsen also mentioned the increase in the number of scientific meetings held during the year in London and the Provinces and paid tribute to the Local Representatives for their efforts in strengthening this aspect of the Society's work. He also referred to the gratifying increase in the number of applications for grants from the Research Fund.

The year saw the welcome return of the possibility of international intercourse between chemists, and the Society was able to welcome chemists from the Dominions and India on the occasion of the Royal Society Empire Scientific Conference, and foreign colleagues at a Conference of the Council of the International Union of Chemistry.

Reference was also made to the forthcoming Centenary Celebrations, and it was reported that the Centenary Appeal now stood at over £18,000.

It was explained that it had not been possible in the time available to prepare the Accounts for presentation, and the Annual General Meeting would therefore be adjourned to a later date when the Accounts would be available.

In conclusion Dr. Simonsen paid tribute to the work of Dr. Martin as General Secretary whose resignation on appointment to the Royal Society had been received with regret, and welcomed Mr. L. R. Batten as the new General Secretary. He also expressed the Council's appreciation of the loyal work of the permanent staff of the Society.

In proposing the adoption of the Report of Council, Dr. G. M. Bennett stressed the supreme importance of the Society as the medium for the publication of papers and said that he hoped that the time would come when this work would have increased to such an extent that the Society would require increased financial assistance for the purpose. That such assistance would be necessary would be an indication of the progress being made in fundamental chemical research and would be a worthy effort on the part of the Society as a publishing body. The proposal was seconded by Dr. E. G. V. Percival who expressed pleasure at the close contact between the Society and its Local Representatives and the interest shown and help given by the Council in fostering the work of the Society in provincial centres. The Report was adopted.

The report of the Scrutators on the ballot for a Vice-President who had not filled the office of

President and for Elected Ordinary Members of Council for Constituencies I and IV was presented and it was declared that the following had been elected :—

Vice-President who has not filled the Office of President : Dr. Joseph Kenyon.

Elected Ordinary Members of Council :.

Constituency I (South-East England) : Dr. Frances M. Hamer, Dr. Frederick E. King, Dr. Henry N. Rydon.

Constituency IV (North-East England) : Dr. George M. Dyson, Dr. Frank R. Goss.

A vote of thanks to the Vice-Presidents, Treasurer, Honorary Secretaries, Council and Committees for their services during the past year was proposed by Dr. Gillam and seconded by Dr. Goss.

The appointment of Auditors was postponed until the Accounts are presented.

The meeting was then adjourned until a date to be announced when the Accounts of the Society for 1946 would be presented.

The Anniversary Luncheon was held at the Dorchester Hotel, Park Lane, at 1 p.m., the President, Professor C. N. Hinshelwood, presiding. 140 Fellows and Guests attended. The toast of " The Chemical Society " was proposed by the principal guest, Viscount Bennett, President of the Royal Society of Arts. In his reply, the President said that although this was the year of the Centenary Celebrations and no effort was being spared to make these Celebrations a success, nevertheless the Annual Meeting of the Society when the work of the year was reviewed was still important for it was by its everyday activities that the Society ultimately was judged. He referred to the gratifying steady increase in the Fellowship and spoke warmly of the work of the Honorary Officers and of Dr. Martin and the permanent staff, and welcomed Mr. Batten as Dr. Martin's successor.

Before a well-attended afternoon meeting the President delivered his Presidential Address entitled " Some Observations on Present Day Chemical Kinetics ". At its conclusion a vote of thanks for his Address with a request that he would allow the Address to be printed in the *Journal* was proposed by Professor Sugden and carried with acclamation.

In the evening some 150 Fellows and friends attended a performance of Ben Jonson's " The Alchemist " staged by the Old Vic Theatre Company.

REPORT OF COUNCIL FOR 1946.

I. CENTENARY CELEBRATIONS.

The Chemical Society is to celebrate in July 1947 the centenary of its foundation. But for the war the Celebrations would have taken place in 1941. The Council appointed a Centenary Celebrations Executive Committee and a number of Sub-Committees to organise the Society's Centenary Celebrations. Preparations are well advanced, and a programme of events has been arranged for three days, July 15th—July 17th, 1947, in London. The Council has noted with satisfaction the offers of assistance from the Society of Chemical Industry and the Royal Institute of Chemistry, and that during the Celebrations the Society will be entertained by His Majesty's Government, the Royal Society, the University of London, Imperial Chemical Industries and others. The Celebrations will be followed by the Eleventh International Congress of Pure and Applied Chemistry, which will be held on July 17th—July 24th, 1947, in London.

Arrangements have been made with the Royal Society of Arts to hold a special joint meeting to commemorate, on February 19th, 1947, the formation of the Chemical Society on February 23rd, 1841. The Lecturer will be Sir Harold Hartley and the subject " A Century of Chemistry ".

Sir Robert Robinson, P.R.S., has accepted the invitation of Council to deliver the Faraday Lecture during the Celebrations.

The Council has decided to make an appeal for a Centenary Fund to be used for the promotion of the international intercourse of chemists.

II. FELLOWSHIP.

1. *Fellowship Statistics.* During 1946, 732 Fellows were elected and 29 reinstated, the corresponding figures in 1945 being 581 and 32, respectively. The Society has lost 1 Fellow on active service, 2 reported missing, 61 by death, 80 by resignation and 1 by removal, making a total loss of 145 as against 152 in 1945. The number of Fellows on December 31st, 1946, was 6920. Of these 3086 are joint members of the three Chartered Bodies and 1051 are joint members of the Chemical Society and Society of Chemical Industry alone. Of those who became joint members of the three bodies in 1946, 297 are new Fellows of the Chemical Society and of those who became joint two-body members 154 are new Fellows. The number of joint members of the three bodies has increased during the year by 327, the number of joint members of the two bodies by 153, and the number of single-body Fellows has increased by 94.

2. *Joint Student Facilities.* During 1946, 42 persons have been granted joint student facilities by the two publishing societies under the Chemical Council scheme.

3. *Honours.* The congratulations of the Society were conveyed to the following Fellows who received during the year the honours indicated:

Professor E. C. Baughan, O.B.E.
Mr. R. B. Bourdillon, C.B.E.
Mr. P. H. Carpenter, C.I.E.
Dr. H. J. Channon, C.M.G.
Professor W. M. Cumming, O.B.E.
Mr. W. A. Damon, C.B.E.
Dr. A. Forster, O.B.E.
Professor W. E. Garner, C.B.E.
Dr. R. N. Garrod-Thomas, C.B.E.
Dr. C. F. Goodeve, Knight Bachelor.
Mr. A. T. Green, O.B.E.
Professor I. M. Heilbron, Knight Bachelor.
Mr. H. Jephcott, Knight Bachelor.
Professor H. D. Kay, C.B.E.
Professor J. E. Lennard-Jones, K.B.E.
Dr. R. P. Linstead, C.B.E.
Professor A. K. Macbeth, C.M.G.
Dr. A. Parker, C.B.E.
Mr. J. D. Pratt, C.B.E.
Mr. S. J. Saint, C.M.G.
Dr. J. H. Schulman, O.B.E.
Dr. E. W. R. Steacie, O.B.E.
Dr. T. W. J. Taylor, C.B.E.
Dr. H. A. Tempany, Knight Bachelor.
Dr. W. H. J. Vernon, O.B.E.
Brigadier O. H. Wansbrough-Jones, O.B.E.
Dr. J. R. H. Whiston, O.B.E.
Mr. E. S. Whitworth, B.E.M. (Military Division).

The Council also conveyed congratulations to Sir Alfred C. G. Egerton on his receiving the Rumford Medal of the Royal Society and to Professor C. K. Ingold on his receiving the Davy Medal of the Royal Society.

4. *Deaths.* The Council learned with profound regret of the death of four Honorary Fellows, Professor A. Béhal, Professor E. J. Cohen, Professor G. N. Lewis, and Professor F. A. H. Schreinemakers.

The Council heard with sorrow of the death on October 28th of Professor Percy F. Frankland who was President of the Society from 1911 to 1913.

III. PUBLICATIONS.

Owing to the shortage of labour at the printers it has not been possible to ensure prompt issue of the Society's publications during 1946. The position has not been improved through shortage of fuel, whereby night shifts have, in many cases, not been possible. It is hoped that some improvement may be effected in the coming year.

1. *The Journal.* During the year, 453 scientific communications were received (compared with 347 in 1945), of which 7 were declined and 1 withdrawn.

The *Journal* for the year occupied 1175 pages (compared with 930 for 1945). It comprised 314 items (compared with 276 for 1945), made up as follows:

Papers (General, Physical, and Inorganic)	51
„ (Organic)	206
Notes	21
Lectures	6
Presidential Address	1
Obituary Notices	27
General Physical Constants	1
Annual General Meeting and Report of the Bureau of Abstracts	1

The Scientific communications published during the year included contributions from Australia (8), New Zealand (4), South Africa (2), Argentina (1), Egypt (7), France (3), India (1), Norway (1), Palestine (1), Sudan (1), and Switzerland (1).

2. *Annual Reports.* Owing to circumstances outside the control of the Society, it was not possible to publish the Annual Reports for 1945 (Vol. XLII) until after the end of 1946.

IV. MEETINGS.

1. *Scientific Meetings.* The Society has held 12 Scientific Meetings in London during 1946. These included 5 lectures and 2 organised discussions. At the other 5 meetings 10 papers were read and discussed.

65 Meetings were held outside London, these included 58 lectures, 1 discussion, 5 meetings for the reading of papers and 1 scientific film display. Of these meetings, 40 were held jointly with local sections of other bodies.

Three official Scientific Meetings were held outside London at Glasgow, at Oxford, and at Edinburgh.

Of special interest was Professor H. C. Urey's visit to this country to deliver the eleventh Liversidge Lecture.

A complete list of meetings is given in Appendix B.

2. *Anniversary Meeting.* A report of the Anniversary Meeting held in Birmingham on April 25th appeared in the *Journal* for May.

This consisted of the 105th Annual General Meeting and Presidential Address, a presentation to Mr. S. E. Carr, formerly General Secretary of the Society, and a reception and luncheon by the University of Birmingham. The cordial thanks of the Council were conveyed to the University authorities and to those responsible for the admirable arrangements that were made.

V. LIBRARY.

The Annual Report of the Joint Library Committee for 1946 appears as Appendix A.

VI. OTHER ACTIVITIES.

1. *Advisory Committee on the Dyson System for Ciphering Chemical Compounds.* During the year proposals by Dr. G. M. Dyson on a new method of ciphering chemical compounds were brought before the Council. An advisory committee under the Chairmanship of Professor A. R. Todd was appointed to examine the proposals, and on the receipt of this report Council asked the International Union of Chemistry to consider Dr. Dyson's proposals at the meeting of the Union to be held in London in July 1947.

The Chemical Society, the Royal Institute of Chemistry, the Society of Chemical Industry, and the Bureau of Abstracts made arrangements to enable Dr. Dyson to describe his proposals at a joint meeting of these bodies on October 21st, 1946. This lecture has been published, and through the generosity of the Royal Institute of Chemistry was made available free of charge to all Fellows of the Society.

2. *Gmelin Handbook.* In November the Council of the Society decided to give scientific support through the Control Commission for Germany to the re-commencement of the Gmelin Handbook.

3. *Visits of Overseas Chemists.* During the summer the Society welcomed chemists who were attending the Royal Society Empire Scientific Conference (June 21st) and members of the Council and Bureau of the International Union of Chemistry (July 25th).

4. *Grants for Research.* During the year Council authorised the payment of research grants amounting to £522 to 30 applicants.

VII. ADMINISTRATION.

1. *Personnel of Council.* At the Annual General Meeting on the 25th April, the following elections were made :—

President	Professor C. N. Hinshelwood.
Vice-Presidents	Dr. R. P. Linstead and Professor S. Sugden.
Honorary Secretaries	Professor D. H. Hey and Dr. J. L. Simonsen.
Ordinary Members of Council	Dr. J. F. J. Dippy, Dr. S. H. Harper, Dr. F. G. Mann, and Dr. C. W. Shoppee.

The retirement of Dr. G. M. Bennett from the office of Honorary Secretary was noted with special regret, and warm appreciation was expressed for his very valuable services to the Society during his term of office, which covered the whole period of the war.

The Council received with regret at their October meeting the resignation of Dr. R. J. W. Le Fèvre from the office of Elected Ordinary Member of Council on his appointment as Professor of Chemistry at the University of Sydney, Australia. The Council invited Dr. F. E. King to fill the vacancy until the next Annual General Meeting.

2. *Local Representatives.* During the year the Council have accepted with much regret a number of resignations from the office of Local Representative. The Council have expressed their thanks to those retiring from office for the valuable services they had rendered to the Society, and have made the following appointments :—

Aberdeen.	Dr. J. M. C. Thompson	in place of	Mr. T. H. Reade.
Cambridge.	Dr. B. Lythgoe	,,	Dr. F. S. Dainton.
Glasgow.	Dr. J. D. Loudon	,,	Dr. J. Bell.
Liverpool.	Mr. L. A. Haddock and Dr. W. B. Whalley	,,	Dr. A. McGookin.
Newcastle.	Dr. Wesley Cocker	,,	Dr. G. H. Christie.
	Dr. F. L. Robinson	,,	Dr. Wesley Cocker.
Oxford.	Dr. F. E. King	,,	Mr. R. P. Bell.
Sheffield.	Dr. A. H. Lamberton	,,	Dr. Brynmor Jones.
Southampton.	Dr. K. R. Webb	,,	Dr. S. H. Harper.

3. *General Secretary.* The Council received with regret the resignation of Dr. D. C. Martin, General Secretary, on his appointment as the Assistant Secretary to the Royal Society. Arrangements were made to retain Dr. Martin's part-time services until the appointment of a successor.

VIII. FINANCE.

1. *Investments.* The following alterations to the Society's investments have been made during the year :—

£150 standing to the credit of Life Composition Fees in General Account, invested in 2½ Savings Bond 1964—1967.

£1200 on General Account, proceeds of the repayment of £1200 Leeds Corporation 3% Stock, reinvested in 2½% Defence Bonds.

£1612 10*s.* 2*d.* 2½% National War Bonds 1945—1947 on Special Reserve Fund was redeemed and reinvested in 2½% Savings Bonds 1964—1967.

£5863 11*s.* 7*d.* 2½% National War Bonds 1946—1948 on Special Reserve Fund converted into 2½% Savings Bonds 1964—1967.

£2100 2½% National War Bonds 1946—1948 on Staff Pensions Fund converted into 2½% Savings Bonds 1964—1967.

Authority was also given for the conversion of :—

£3825 1*s.* 6*d.* 3% Local Loans on General Purposes Account into 2½% Treasury Stock 1975, or after.

£4741 4*s.* 10*d.* 3% Local Loans on Research Fund Account into 2½% Treasury Stock 1975, or after.

£3344 3*s.* 4*d.* 3% Local Loans on Publications Fund into 2½% Treasury Stock 1975, or after.

£1520 14*s.* 3*d.* Cardiff Corporation 3% Redeemable Stock 1914—54 on General Account into Cardiff Corporation Redeemable Stock 1966—1971 at £99 per cent.

The following stock was redeemed and not reinvested :—

£391 17*s.* 4*d.* 3% Local Loans on Staff Pensions Fund Account.

The bequest of £500 from the late Sir Martin Forster has been placed in the Research Fund of the Society and invested in 3% Defence Bonds.

2. *Annual Subscription.* With increased activities following the end of the war, together with increased costs of printing and administration, the Society was faced with the very rapid depletion in the amount of the Reserve Fund followed by the prospect of an annual deficit. The Council therefore proposed

> "That as from January 1st, 1947, the amount of the annual subscription be increased from three pounds (£3) to three pounds ten shillings (£3 10*s.*), and that a corresponding increase be made in the amount of the life composition fee."

This proposal was confirmed at an Extraordinary Meeting of the Society on July 28th, 1946.

In accordance with Bye-Law 8c, the Council altered the amount of the Subscription payable by Fellows under 25 years of age from one pound ten shillings (£1 10*s.*) to one pound fifteen shillings (£1 15*s.*).

3. *Insurances.* Fire insurances on the Library, and on stocks of publications, have been increased by appropriate amounts.

4. *Contributions.* The Council received towards the cost of publications £1000 from the Chemical Council and through the Royal Society £750 from the Government Grant.

The Faraday Society is now represented on the Chemical Council, and will from 1945 onwards contribute towards the cost of the Library a sum based on its membership, with due allowance for overlap with the three Constituent Bodies.

5. *Staff.* New Staff salary gradings have been applied to the Society's Staff, and these take into account consolidation of war bonuses.

6. *Joint Pensions and Life Assurance Scheme.* The Council has accepted a scheme initiated by the Chemical Council and arranged by a Conference of Scientific Societies for the provision of Pensions and Life Assurance for the staff on a contributory basis. Those members of the staff already participating in the existing scheme have been given the option of remaining in the existing scheme if they so desire.

IX. RELATIONS WITH OTHER BODIES.

(1) *Representatives of the Society on other Bodies.*

During 1946 the Society was represented as follows :—

Anglo-Soviet Scientific Collaboration Sub-Committee : Sir John Russell.

Association of British Chemical Manufacturers :

Joint Technical Committee on Patents : Dr. J. T. Hewitt.

Barker Committee :

Formed to support the publication of the Barker Index of the characteristic angles of crystalline compounds : Dr. G. M. Bennett.

Bristol University Court : Professor F. G. Donnan.

British National Committee for Chemistry : Professor W. N. Haworth, Sir Ian M. Heilbron, Dr. W. H. Mills.

British Standards Institution. Technical Committees :

Co-ordinating the work of the Divisional Councils in regard to any British Standard which may be issued in future for units, conversion factors, fundamental formulæ, values for properties of materials, etc. : Professor S. Sugden.

Standardisation of Microchemical Apparatus: Professor H. V. A. Briscoe, Dr. H. D. K. Drew.
Specifications for Materials and Plant used in Electroplating: Dr. U. R. Evans.
Standardisation of Scientific Glassware: Mr. F. R. Ennos.
Standards for use in Dairying Chemistry: Mr. Eric Voelcker.
Standardisation of Letter Symbols: Professor S. Sugden.
Technical Committee C/17 Viscosity: Dr. A. E. Dunstan.

Bureau of Abstracts.

Directors and Members: Dr. G. M. Bennett, Mr. F. P. Dunn, Dr. E. B. Hughes, and Dr. E. H. Rodd.
Members: Mr. R. P. Bell, Professor H. V. A. Briscoe, Professor G. A. R. Kon, Professor W. Wardlaw.

Chemical Council: Dr. G. M. Bennett, Professor C. N. Hinshelwood, Professor W. Wardlaw, Mr. F. P. Dunn.

City and Guilds of London Institute: Professor H. V. A. Briscoe.

Faraday Society—Colloid Committee: Dr. G. S. Hartley.

International Union of Chemistry:

Committee for the Reform of the Nomenclature of Organic Chemistry: Professor C. S. Gibson.

Joint Library Committee: Professor H. Bassett, Dr. L. Brady, Professor C. H. Desch, Mr. M. B. Donald, Mr. F. P. Dunn, Dr. H. J. Emeléus, Dr. P. Haas, Dr. T. A. Henry, Dr. J. R. I. Hepburn, Professor D. H. Hey, Dr. Harold King, Professor G. A. R. Kon, Professor E. E. Turner, Professor W. Wardlaw.

Lawes Agricultural Trust:

Committee of Management: Professor W. N. Haworth.

Parliamentary and Scientific Committee: Professor C. N. Hinshelwood, Professor D. H. Hey.

Royal Society:

Joint Standing Committee for Symbols and Abbreviations: Professor C. W. Davies, Professor S. Sugden.

Safeguarding of Industries Committee: Professor C. S. Gibson.

Yorkshire Council for Further Education:

Advisory Committee for Chemistry in South and East Yorkshire: Professor R. D. Haworth, Dr. Brynmor Jones.

(2) *Representatives of the Society at Public Functions.*

Council and Bureau of the International Union of Chemistry, London, July 24th—27th: Professor W. Wardlaw.
Vingtième Congrès de Chimie Industrielle de la Société de Chimie Industrielle, September 22nd—28th: Dr. F. A. Freeth.
Ramsay Dinner, Glasgow, December 6th: Sir Ian M. Heilbron.
Installation of the Rt. Hon. The Earl of Harewood as Chancellor of the University of Sheffield, June 25th: Professor R. Whytlaw Gray.

APPENDIX A.

ANNUAL REPORT OF THE JOINT LIBRARY COMMITTEE, 1946.

The increase in the use of the Library which was recorded in the last report has continued in 1946. Attendances by readers showed an increase of 2195 and books borrowed of 1444. Photostat copying reached a total of 4174 pages, this being an increase of 144 on the previous year, and telephone enquiries to the number of 1560 were dealt with, this being about the same figure as for 1945.

Books added to the Library totalled 254, of which 99 were presented. 593 volumes of periodicals and 181 pamphlets were also added. The number of volumes contained in the Library is now 47,863, of which 14,330 are books and 33,533 volumes of periodicals.

Analysis.

	Attendances.	Books borrowed.	Books. added.	Volumes of periodicals.	Pamphlets.
1946	11,370	9548 (3396 by post)	254	593	181
1945	9,175	8104 (2900 by post)	267	476	97
1938 .....A...	8,507	5948 (1697 by post)	250	744	283

(The figures for 1938, the last complete pre-war year, are given for comparison.)

Among the donations to the Library was a gift of eight historical books from Sir Wyndham Dunstan, and also some useful sets of periodicals from Dr. F. A. Freeth. To these gentlemen and all others who have added to the value of the Library by gifts of books the Committee is most grateful.

All the volumes which were sent to the provinces for safety during the war have now been returned, and are available for use.

Following their visit in 1945, Dr. H. McCombie and the Librarian paid another visit to Germany in the spring. The team was strengthened by the addition of Professor H. J. Emeléus and Mr. M. B. Donald. Three weeks intensive search in the British zone resulted in the acquisition of nearly 150 books and some 50 volumes of periodicals, which did not arrive until the end of the year, and are not included in the totals shown above.

The Committee wishes to record its thanks to Sir Norman Haworth for his interest in the reading-room accommodation, which resulted in the installation of fluorescent lighting.

Modification in the arrangement of the Reading Room has resulted in some additional accommodation for readers, and the Committee is continuing its efforts to improve both the accommodation and the availability of books as far as the present building allows. Unfortunately, such rearrangements necessarily cause inconvenience to readers by making fewer books directly accessible.

The List of German Books on chemical and cognate subjects published from 1939 to 1946, compiled by Dr. Hamilton McCombie, D.S.O., M.C., and the Librarian, has now been published by the Chemical Council from which body a copy can be obtained, free of charge, by members of any Society represented on the Chemical Council.

APPENDIX B.

MEETINGS HELD DURING 1946.

IN LONDON.

January 17th, *Tilden Lecture*, " Substitution ", by Professor E. D. Hughes; February 7th, *Meeting* for reading papers; March 7th, *Pedler Lecture*, " Synthesis in the Study of Nucleotides ", by Professor A. R. Todd; April 4th, in the Lecture Hall of the Institution of Mechanical Engineers, *Discussion* on " Some Aspects of the Chemistry of Macromolecules ", opened by Professor H. W. Melville; May 16th, *Meeting* for reading papers; July 25th, *Extraordinary General Meeting*; October 3rd, *Meeting* for reading papers; October 17th, *Meeting* for reading papers; October 21st, at the London School of Hygiene and Tropical Medicine (joint meeting with the Royal Institute of Chemistry, the Society of Chemical Industry, and the Bureau of Abstracts), *Lecture*, " A New Notation for Organic Chemistry ", by Dr. G. M. Dyson; November 7th, *Discussion* on " Nitration ", opened by Dr. G. M. Bennett; November 21st, *Meeting* for reading papers; December 5th, *Tilden Lecture*, " Macromolecules Synthesised by Micro-organisms," by Professor M. Stacey; December 18th, at the Royal Institution, *Liversidge Lecture*, " Some Problems in the Separation of Isotopes ", by Professor H. C. Urey.

OUTSIDE LONDON.

Aberdeen. At Marischal College (Joint meetings with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry); October 25th, *Lecture*, " Microscopy with Electrons and *X*-Rays," by Professor G. D. Preston; November 29th, *Lecture*, " Some Developments in the General Methods of Organic Chemistry," by Professor F. S. Spring; December 17th, *Lecture*, " Mechanism of Elimination and Substitution Reactions ", by Dr. F. W. Peaker.

Birmingham. At the University: February 12th, *Pedler Lecture*, " Synthesis in the Study of Nucleotides ", by Professor A. R. Todd; April 25th, The Hundred and Fifth *Annual General Meeting* of the Society.

Bristol. At the University (Joint meetings with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry); February 7th, *Lecture*, " The Chemistry of Penicillin ", by Professor W. Baker; October 10th, *Lecture*, " Recent Advances in Plastics ", by Mr. N. J. L. Megson; October 24th, *Lecture*, " The Work of the Forensic Science Laboratories ", by Mr. E. B. Parks; November 7th, *Lecture*, " Electron Transfer Reactions in Solution ", by Professor M. G. Evans; (Joint meeting with the local sections of the Royal Institute of Chemistry, the Society of Chemical Industry, and the Institution of Chemical Engineers); December 5th, *Lecture*, " Drying with Activated Alumina ", by Mr. A. J. Carter.

Cambridge. October 18th (Joint meeting with the Cambridge University Chemical Society) at the University, *Lecture*, " Aromatic Nitration ", by Professor C. K. Ingold.

Edinburgh. At the North British Station Hotel (Joint meetings with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry): February 22nd, *Lecture*, " Some Problems in Polysaccharide Chemistry ", by Professor E. L. Hirst; March 22nd, *Lecture*, " Trace Elements in Agriculture ", by Dr. W. G. Ogg; October 10th, *Lecture*, " Heavy Chemicals ", by Dr. J. P. Baxter; November 21st, *Lecture*, " Some Developments in the General Methods of Organic Chemistry ", by Professor F. S. Spring; at the University: October 29th (Joint meeting with the Edinburgh University Chemical Society and the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry), *Lecture*, " Some Observations on Biological Oxidation and Reduction ", by Dr. D. J. Bell; December 19th, *Official Meeting* of the Society and *Liversidge Lecture*, " Some Problems in the Separation of Isotopes ", by Professor H. C. Urey.

Eire. At University College, Dublin: February 26th, *Lecture*, " The Structure and Enzymic Synthesis of Starch ", by Professor W. N. Haworth; November 20th (Joint

meeting with the local section of the Royal Institute of Chemistry), *Meeting* for reading of paper by Dr. T. G. Brady on "Biochemical Microtechnique"; December 9th, *Lecture*, "The Use of the Mass Spectrometer in Following the Course of Gas Reactions", by Professor H. C. Urey.

Exeter. At the Washington Singer Laboratories, March 1st, *Lecture*, "Colloids and Rheology—Introductory", by Dr. E. W. Mardles; March 8th, *Lecture*, "The Stability of Colloidal Systems", by Dr. E. W. Mardles; November 25th, *Lecture*, "Structural Inorganic Chemistry", by Professor W. Wardlaw.

Glasgow. At the University, February 15th, *Official Meeting* of the Society, *Tilden Lecture*, "Some Recent Developments in the Chemistry of Free Radicals", by Dr. W. A. Waters; November 15th (Joint meeting with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry), *Lecture*, "Melting and Other Phase Changes", by Professor A. R. Ubbelohde; at the Royal Technical College, Glasgow, October 25th (Joint meeting with the Alchemists' Club and the Andersonian Chemical Society), *Lecture* by Dr. H. J. T. Ellingham on the organised services provided for the chemist by the three Chartered Chemical Bodies; October 25th (Joint meetings with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry), *Lecture*, "Electrolysis as an Industrial Process", by Dr. H. J. T. Ellingham; November 1st, *Lecture*, "Atomic Energy", by Professor P. I. Dee.

Leeds. At the University, March 5th (Joint meeting with the Leeds University Chemical Society), *Lecture*, "Crystal Analysis as a Clue to Chemical Problems", by Dr. K. Lonsdale, preceded by scientific films "Handle with Care" and "Buried Treasure"; December 16th, *Lecture*, "Isotopes", by Professor H. C. Urey.

Liverpool. At the University, February 21st, *Lecture*, "The Chemical Investigation of some New Therapeutic Agents", by Dr. F. E. King; November 13th (Joint meeting with the local sections of the Royal Institute of Chemistry, the Society of Chemical Industry, the British Association of Chemists, and the University Chemical Society), *Lecture*, "Some Aspects of Infra-red Measurements", by Dr. H. W. Thompson; November 27th (Joint meeting with the local section of the Royal Institute of Chemistry), *Lecture*, "The Development and Industrial Application of Wetting Agents", by Mr. A. V. Billinghame; December 6th (Joint meeting with the local sections of the Royal Institute of Chemistry, the Society of Chemical Industry, and the British Association of Chemists), *Lecture*, "Atomic Energy", by Dr. J. P. Baxter; At Radiant House, December 4th, *Scientific Films*, entitled "The Story of D.D.T.", "Universities at War", "Synthetic Rubber", "Penicillin Manufacture", and "It Comes from Coal".

Manchester. At the University, January 24th (Joint meeting with the local section of the Royal Institute of Chemistry), *Tilden Lecture*, "Some Recent Developments in the Chemistry of Free Radicals", by Dr. W. A. Waters; March 14th, *Meeting* for reading papers; May 7th, *Lecture*, "Recent Developments in Polynucleotide Chemistry", by Professor J. M. Gulland; October 24th (Joint meeting with the local section of the Royal Institute of Chemistry and the Manchester University Chemical Society), *Lecture*, "The Chemistry of Penicillin", by Professor W. Baker; November 15th (Joint meeting with the Manchester Federation of Scientific Societies), *Lecture*, "The Chemistry of Plant Gums and Related Substances", by Professor E. L. Hirst and Dr. J. K. N. Jones; December 12th, *Meeting* for reading papers; at the Engineers' Club, February 27th (Joint meeting with the local section of the Royal Institute of Chemistry), *Lecture*, "What Industry Expects from the Chemist", by Dr. C. J. T. Cronshaw.

Newcastle and Durham. At King's College, Newcastle-upon-Tyne, February 22nd, *Bedson Club Lecture*, "Structural Inorganic Chemistry", by Professor W. Wardlaw; March 1st, *Meeting* for reading papers; May 10th, *Bedson Club Lecture*, "Whither Chemistry?", by Sir Robert Pickard; October 11th, *Meeting* for reading papers; November 22nd, *Bedson Club Lecture*, "Insecticides", by Dr. J. L. Simonsen.

Northern Ireland. At Queen's University, Belfast, March 4th, *Lecture*, "The Structure and Enzymic Synthesis of Starch", by Professor W. N. Haworth; December 10th, *Lecture*, "Isotopes", by Professor H. C. Urey.

North Wales. At University College, Bangor, February 21st (Joint meeting with the University College of North Wales Chemical Society), *Lecture*, " The Structure of Boron Hydrides and Related Compounds ", by Mr. R. P. Bell; November 21st (Joint meeting with the University College of North Wales Chemical Society and the University of Liverpool Chemical Society), *Lecture*, " Nitration in Sulphuric Acid ", by Dr. G. M. Bennett.

Nottingham. At University College, January 25th, *Lecture*, " Colchicine, its Chemistry and some Biological Effects ", by Professor J. W. Cook; November 21st (Joint meeting with the University College Physical and Chemical Society), *Lecture*, " Some Aspects of the Chemistry of Paludrine ", by Dr. F. L. Rose.

Oxford. At the Physical Chemistry Laboratory, South Parks Road, Oxford, June 6th, *Official Meeting* of the Society held jointly with the Oxford University Alembic Club, *Discussion*, on " The Chemistry of Anti-bacterial Substances ", opened by Sir Robert Robinson.

St. Andrews and Dundee. At University College, Dundee, January 25th, *Lecture*, " Chemical Products from Seaweeds ", by Dr. E. G. V. Percival; February 18th, *Lecture*, " Chemical Research and the Army ", by Dr. D. C. Martin; April 15th, *Lecture*, " Rheology —the Study of the Deformation and Flow of Matter ", by Dr. Scott Blair; October 25th, *Lecture*, " Applied Photography ", by Mr. F. W. Coppin; at United College, St. Andrews, November 15th (Joint meeting with the St. Andrews University Chemical Society), *Lecture*, " Applications of the Hofmann Reaction to the Synthesis of Heterocyclic Compounds ", by Professor F. S. Spring; at University College, Dundee, November 25th, *Lecture*, " A Chemist Abroad—Student Days at Zürich ", by Professor J. Read.

Sheffield. At the University (Joint meetings with the University Chemical Society), February 8th, *Lecture*, " Light Absorption from a Chemical Standpoint ", by Mr. E. J. Bowen; March 8th, *Lecture*, " Some Aspects of the Chemistry of Mono- and Di-sulphide Links ", by Professor F. Challenger; May 3rd, *Lecture*, " Vitamin A ", by Professor R. A. Morton; October 24th, *Lecture*, " Synthetic Approach to the Nucleotides ", by Professor A. R. Todd; November 8th, *Lecture*, " Some Applications of Infra-red Measurements ", by Dr. H. W. Thompson; October 17th (Joint meeting with the local section of the Royal Institute of Chemistry, the Sheffield Metallurgical Association, and The University Chemical Society), *Lectures*, " Principles of Polarography ", and " The Applications of Polarographic Analysis ", by Professor J. Heyrovsky; November 21st (Joint meeting with the South Yorkshire section of the Royal Institute of Chemistry, the Sheffield Metallurgical Association, and the University Chemical Society), *Lecture*, " Chemistry in the Metallurgical Industries ", by Dr. C. H. Desch.

South Wales. At University College, Swansea (Joint meetings with the University College of Swansea Chemical Society), January 28th, *Lecture*, " The Separation of Isotopes and Thermal Diffusion ", by Professor J. Kendall; November 1st, *Lecture*, " Homolytic Reactions ", by Professor D. H. Hey; at University College, Cardiff, February 22nd (Joint meeting with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry), *Lecture*, " Recent Work on Soil Biochemistry ", by Dr. J. H. Quastel.

Southampton. At University College (Joint meetings with the University College Chemical Society), May 3rd, *Lecture*, " Penicillin ", by Dr. A. H. Cook; May 17th, *Lecture*, " Nucleoproteins ", by Professor J. M. Gulland; May 24th, *Lecture*, " Structural Inorganic Chemistry ", by Professor W. Wardlaw; at Municipal College, Portsmouth, October 17th (Joint meeting with the Portsmouth and District Chemical Society and the University College of Southampton Chemical Society), *Lecture*, " Chemical Aspects of Work on Atomic Fission ", by Professor H. J. Emeléus.

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